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CONTRACT NO: DAMD17-87-C-7202

TITLE: HUMAN ADAPTATION TO THE TIBETAN PLATEAU

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CONTRACTING ORGANIZATION: University of Colorado
Health Sciences Center
4200 East Ninth Avenue, Box B-133
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REPORT DATE: August 12, 1991

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION University of Colorado Health Sciences Center 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) 4200 East Ninth Avenue Denver, Colorado 80262	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING / SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER Contract No. DAMD17-87-C-7202
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21702-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 0602787A; PROJECT NO. 3M1-62787A879; TASK NO. BC; WORK UNIT ACCESSION NO. 085

11. TITLE (Include Security Classification)
HUMAN ADAPTATION OF THE TIBETAN PLATEAU

12. PERSONAL AUTHOR(S)
Lorna Grindlay Moore, Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final Report	FROM 8/7/87 TO 6/30/91	1991 August 12	

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	High altitude; O_2 transport; hypoxia ventilation; blood flow; altitude illness; exercise; RAIII
06	05		
06	04		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Humans have lived at high altitude for longer periods of time on the Tibetan Plateau than elsewhere in the world, thus providing opportunity to investigate the physiologic effects of long-term (years to generation) duration of high altitude exposure. This has military importance because persons are stationed at high altitudes for extended periods of time and experience marked decrements in performance and health. Knowledge as to the physiologic traits required for successful high-altitude adjustment is important for the selection of personnel resistant to the ill effects of high altitude and for the treatment of afflicted individuals. The results of this research supported the underlying hypothesis that Tibetans are better-adapted to high altitude than acclimatized newcomers in Tibet or than persons elsewhere in the world as judged from literature reports. The Tibetans' superiority was evidenced by: greater maximal oxygen uptake, higher work capacity, increased greater vital capacity and lung volume, decreased alveolar-arterial oxygen diffusion gradient, absence of hypoxic pulmonary vasoconstriction, increased cardiac output and increased tissue oxygen utilization. In addition, Tibetans are resistant to the development of Chronic Mountain Sickness. Compared to healthy controls, persons with Chronic Mountain Sickness breathe less and have lower arterial oxygen saturations than healthy persons, due to the absence of hypoxic ventilatory sensitivity and greater hypoxic ventilatory depression, and likely suffer from decrements in nocturnal brain oxygen delivery.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Mrs. Virginia Miller	22b. TELEPHONE (Include Area Code) 301-619-7325 / 22c. OFFICE SYMBOL SGRD-RMI-S

DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

FOREWORD

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Lorna Findley Moore 8/12/91

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INTRODUCTION

The overall purpose of this project was to determine whether Tibetans possessed special abilities to transport and utilize oxygen and whether some Hans (Chinese) lacked the necessary oxygen transport characteristics to enable successful adaptation to high altitude.

The Tibetans' physiological response to high altitude is of interest because the Tibetans are likely to be the world's highest and longest-resident high-altitude population. Hence, the Tibetans represent a "gold standard" by which to determine the physiological responses that are most adaptive for prolonged residence at high altitude and to assess whether genetic adaptation to high altitude has taken place. Prior to this contract, there had been little systematic investigation of the Tibetans' physiological responses to high altitude.

SUMMARY OF RESEARCH RESULTS

The three years' support provided by USAMRDC Contract No. DAMD 17-87-C7202 was used to conduct field studies in Tibet in 1987, 1988 and 1990. The purpose, major findings and publications emanating from each of these field studies are summarized below.

1) Fall 1987 Studies

The purpose of the Fall 1987 studies was to compare the integrated performance of the oxygen transport system in lifelong residents of high altitude with that of acclimatized newcomers. The studies were conduced in Lhasa (elev 3658 m or 12,070 ft) where both lifelong residents of high altitude (Tibetans) and migrants from low altitude (Han "Chinese") are readily available for study. More than 100 subjects were studied between 24 August and 20 October, 1987. Measurements included tests of ventilatory control, chest circumferences and vital capacities in men and women; studies of exercise performance and brain blood flow in men; and assessment of uterine blood flow in pregnant women.

The results supported the hypothesis that lifelong Tibetan residents of high altitude had superior overall functioning of the oxygen transport system in comparison with Han acclimatized newcomers.

a) The Tibetans had significantly higher maximal oxygen uptakes and work capacities. Their greater exercise performance was related to larger chest circumferences and forced vital capacities at rest and better maintenance of arterial oxygen saturation during exercise, suggesting that the Tibetans benefited from a greater lung diffusing capacity.

b) Tibetans had greater acute hypoxic and hypercapnic ventilatory responsiveness than the Hans. Unlike other lifelong high-altitude residents, the Tibetans appeared to retain ventilatory responsiveness to hypoxia. This, in turn, was likely a factor in protecting Tibetans from the development of Chronic Mountain Sickness. We found fewer Tibetans than Hans among patients with Chronic Mountain Sickness and that the hypoventilation of Chronic Mountain Sickness was due in large part to a reduced or blunted hypoxic ventilatory response and a depressant effect of ambient hypoxia

on ventilation. Their blunted hypoxic ventilatory response and presence of hypoxic ventilatory depression was not reversed with intravenous infusion of naloxone, implying that increased endogenous opioid production was not involved.

c) In studies of pregnant women conducted during the same study period but supported by another source, we observed that pregnant Tibetans had greater uterine arterial blood flow velocity but equal ventilation and levels of arterial oxygen saturation when compared with pregnant Hans. That the Tibetan women produced heavier birth weight infants and had fewer complications of pregnancy and neonatal life than the Hans suggested that greater uterine blood flow may have augmented uterine oxygen delivery and fetal growth so as to preserve Tibetan birth weight at optimal, sea-level values.

After the completion of the 1987 studies, Sun Shin-Fu, Director of the Tibet Institute of Medical Sciences, was invited to come to the United States for three months in order to help analyze data and write up research results. Dr. Dolkar, Director of the Tibet Autonomous Region Health Bureau was also invited to visit Denver while attending World Health Organization meetings in Washington, D.C. in the Spring 1988.

2) Fall 1988 Studies

The purpose of the Fall 1988 studies was to compare breathing and brain blood flow during sleep in healthy young Tibetans *versus* Hans and in persons Chronic Mountain Sickness *versus* age-matched controls. Between 15 October and 30 November, 1988, studies were conducted in more than 50 subjects during wakefulness and sleep.

Results indicated that healthy young Tibetan as well as Han young men equally well-maintained their breathing and arterial oxygen saturation during sleep but that persons with Chronic Mountain Sickness experienced profound reductions in brain oxygen delivery.

a) Healthy young Tibetan and Han men did not exhibit significant numbers of sleep-disordered breathing episodes (hypopneas + apneas). When such episodes occurred, both the Tibetan and Han young men raised their carotid arterial blood flow velocity, suggesting that the hypoxia and hypercapnia raised brain blood flow and compensated for the reduction in arterial oxygen saturation experienced.

b) Patients with Chronic Mountain Sickness experienced significant numbers of sleep-disordered breathing episodes and therefore sustained large falls in arterial oxygen saturation. Moreover, they did not increase their brain blood flow to compensate for the fall in arterial oxygen saturation and thus underwent severe decrements in brain oxygen delivery while asleep.

Sun Shin-Fu and Tarshi Droma, the Director and research physician at the Tibet Institute of Medical Sciences, were invited to come to the University of Colorado at the completion of the 1988 project for a 6-month period to aid in data analysis and planning the next year's research program. Because the volume of data generated required additional time for analysis, we requested that their stay be extended to 12 months.

3) Spring 1990 Studies

The purpose of the 1990 project was twofold. One purpose was to test the hypothesis that Tibetans achieved greater oxygen transport with decreased sympathetic nervous system stimulation and increased parasympathetic nervous system tone. A second purpose was to determine whether decreased pulmonary vasoreactivity in the Tibetans reduced pulmonary arterial pressure and workload of the heart to enable an increased cardiac output. Between 27 May and July 1, 1990, measurements were completed in 11 Tibetans and 11 Hans on multiple occasions during rest and exercise.

In support of our study hypotheses, the results indicated that the Tibetans achieved greater maximal oxygen uptake with less sympathetic and proportionally more parasympathetic stimulation than the Hans and at remarkably low pulmonary arterial pressures.

a) Beta-sympathetic blockade with propranolol decreased heart rate and parasympathetic blockade with atropine increased heart rate in both groups. However, the decrease in heart rate during exercise was greater in Hans compared with Tibetans and the increase in heart rate with atropine was greater in the Tibetans than the Hans. Thus the Hans appear to be more reliant upon sympathetic activation during exercise whereas the Tibetans appear to be more reliant upon parasympathetic activation. Sympathetic activation can be viewed as an error signal which would be minimized in well-adapted individuals in whom other factors serve to raise cardiac output and/or tissue oxygen utilization.

b) Five healthy Tibetans were studied after right heart catheterization. The Tibetans had remarkably low pulmonary artery pressures. Values averaged 14 mmHg, similar to the sea level norm of 15 mmHg and markedly lower than the 24-28 mmHg range of average values seen in North and South American residents of 3 - 4000 m. The absence of pulmonary hypertension in these healthy Tibetans indicated that pulmonary hypertension is not universal among high-altitude residents and may be maladaptive insofar as it limits cardiac output and exercise performance, and leads to eventual right heart failure. That the Tibetans do not exhibit pulmonary hypertension indicates a truly remarkable degree of adaptation in this high-altitude population.

Dr. Zhuang Jianguo, a research physician at the Tibet Institute of Medical Sciences, was invited to come to the University of Colorado at the completion of the 1990 project for a 4-month period to aid in data analysis and preparation for publication.

CONCLUSIONS

The results obtained from the 1987, 1988 and 1990 studies supported the underlying hypothesis that lifelong Tibetan residents compared to Han acclimatized newcomers of high altitude evidenced superior oxygen transport and/or utilization.

a). Healthy young Tibetans have greater maximal oxygen uptake than healthy young Hans, indicating improved overall functioning of the oxygen transport system. Study results implicated increased vital capacity and lung volume, decreased alveolar-arterial oxygen diffusion gradients, absence of hypoxic pulmonary vasoconstriction,

increased cardiac output and increased tissue oxygen utilization as responsible for the Tibetans' greater oxygen transport.

b). Persons with Chronic Mountain Sickness breathe less and have lower arterial oxygen saturations than healthy persons during the day and especially during the night. Their decreased ventilation is due to the absence of hypoxic ventilatory sensitivity and greater hypoxic ventilatory depression. A widened arterial-alveolar oxygen gradient further worsens hypoxemia in persons with added lung disease.

c). Full-term Tibetan infants weigh more at birth than term Han babies or babies born at similar altitudes elsewhere in the world. The Tibetans' resistance to fetal growth retardation is likely due to greater oxygen delivery *in utero* resulting from greater blood volume expansion, uterine blood flow and blood flow redistribution to favor the uterine circulation.

LIST OF PUBLICATIONS

Publications are listed below that resulted from the research conducted in 1987, 1988 and 1990 that was supported by USAMRDC Contract No. DAMD 17-87-C7202 as well from research sponsored by other federal agencies. The complete publications are included at the end of this appendix.

1. Fall 1987 studies

Sun S, JG Zhuang, TS Droma, JX Tao, SY Huang, RE McCullough, RG McCullough, CS Reeves, JT Reeves, LG Moore. Higher ventilatory drives in Tibetan than Han male residents of Lhasa. Am Rev Resp Dis (Suppl) 137:410, 1988.

Sun S, JG Zhuang, TS Droma, JX Tao, SY Huang, RE McCullough, RG McCullough, CS Reeves, JT Reeves, LG Moore. Higher exercise capacities in Tibetan than Han male residents of Lhasa (3658 m). FASEB J 2:A1281, 1988.

Sun SF, TS Droma, JG Zhuang, JX Tao, SY Huang, RG McCullough, RE McCullough, CS Reeves, JT Reeves, JT Reeves, LG Moore. Greater maximal 0_2 uptakes and vital capacities in Tibetan than Han male residents of Lhasa (3658 m). Resp Physiol 79:151-162, 1990.

Moore LG. High altitude populations: Overview. In: Hypoxia: The Adaptations. JR Sutton, G Coates, J Remmers (eds). Philadelphia, BC Decker Inc, pp 50-52, 1990.

Moore LG and SF Sun. Physiological adaptation to hypoxia in Tibetan and acclimatized Han residents of Lhasa (3658 m). In: Hypoxia: The Adaptations. JR Sutton, G Coates, J Remmers (eds). Philadelphia, BC Decker, Inc, pp 66-71, 1990.

Huang SY, SF Sun, TS Droma, JG Zhuang, JX Tao, RG McCullough, RE McCullough, AJ Micco, JT Reeves and LG Moore. Internal carotid arterial flow velocity during exercise in Tibetan and Han residents of Lhasa (3658 m). Submitted, J Appl Physiol, 1991.

2. Fall 1988 studies

Sun S, SY Huang, TS Droma, JG Zhuang, JX Tao, RG McCullough, RE McCullough, JT Reeves, LG Moore. Decreased ventilation and hypoxic ventilatory responsiveness are not reversed by nalaxone in Lhasa residents with chronic mountain sickness. FASEB J 3:A839, 1989.

Sun SF, CK Pickett, RG McCullough, SA Zamudio, A Micco, TS Droma, JG Zhuang, Y Ping, A Cymerman and LG Moore. Chronic mountain sickness (CMS): Breathing and brain flood flow during sleep. FASEB J 4:A414, 1990.

Sun SF, SY Huang, JG Zhuang, TS Droma, G Banden, RG McCullough, A Cymerman, JT Reeves and LG Moore. Decreased ventilation and hypoxic ventilatory responsiveness

are not reversed by naloxone in Lhasa residents with chronic mountain sickness. Am Rev Resp Dis 142:1294-1300, 1990.

Moore LG, JG Zhuang. RG McCullough, A Cymerman, TS Droma, SF Sun, Y Ping and RE McCullough. Increased lung volumes in Tibetan high altitude residents. Am J Phys Anthro 12 (supplement): 341, 1991.

Droma TS, RG McCullough, RE McCullough, JG Zhuang, A Cymerman, SF Sun, JR Sutton, LG Moore. Increased vital and total lung capacities in Tibetan compared to Han residents of Lhasa (3658 m). Am J Phys Anthro, In Press, 1991.

3. Spring 1990 studies

McCullough RG, RE McCullough, JG Zhuang, TS Droma, SF Sun, A Cymerman, Jr Sutton, G Rapmund, LG Moore. Increased total lung capacities in Tibetan compared to Han residents of high altitude. Hypoxia '91 (In Press).

Groves BM, JR Sutton, TS Droma, RG McCullough, G Rapmund, SF Sun, JG Zhuang, RE McCullough and LG Moore. Absence of hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. Hypoxia '91 (In Press).

Zhuang JG, TS Droma, JR Sutton, B Groves, G Rapmund, C James, SF Sun, and LG Moore. Sympathetic and parasympathetic influences during exercise in Tibetan and Han ("Chinese") residents of Lhasa (3658 m). Hypoxia '91 (In Press).

Sutton JR, BM Groves, RE McCullough, RG McCullough, TS Droma, JG Zhuang, G Rapmund, SF Sun, and LG Moore. Oxygen transport in Tibetan residents of Lhasa 3658 m. Hypoxia '91 (In Press).

4. Publications resulting from research sponsored by other agencies

National Science Foundation

Droma ZX, SF Sun, JG Zhuang, SY Huang, LG Moore. Fetal growth and maternal 0_2 supply in Tibetan and Han residents of Lhasa (3658 m). FASEB J 3:A987, 1989.

Zamudio SA, TS Droma, TE Dahms, SK Palmer and LG Moore. Uterine blood flow, vascular resistance and blood volume during high altitude pregnancy. FASEB J 4:A414, 1990.

Moore LG. Maternal 0_2 transport and fetal growth in Colorado, Peruvian, and Tibetan populations. Am J Physical Anthropology. 78:274, 1989.

Moore LG. Maternal 0_2 transport and fetal growth in Colorado, Peruvian, and Tibetan populations. Am J Hum Biol 2:627-638, 1990.

Zamudio SA, TS Droma, SK Palmer, J Berman, TE Dahms, RE McCullough, RG McCullough and LG Moore. Blood volume expansion and pregnancy outcome in high altitude pregnancy. Am J Phys Anthro 12 (Suppl):187, 1991.

Zamudio SA, SK Palmer, J Berman, RE McCullough, RG McCullough and LG Moore. Circulatory changes in normal versus hypertensive pregnancy at high altitude. Hypoxia '91, In press, 1991.

National Heart, Lung and Blood Institute

Wolfel EE, BM Groves, GA Brooks, GE Butterfield, RS Mazzeo, LG Moore, JR Sutton, PR Bender, TE Dahms, RE McCullough, RG McCullough, SY Huang, SF Sun, RF Grover, HN Hultgren and JT Reeves. Oxygen transport during steady-state sub-maximal exercise in chronic hypoxia. J Appl Physiol 70(3): 1129-1136, 1991.

APPENDIX I

Publications resulting to date from this research principally based on 1987 field studies.

Sun S, JG Zhang, ZX Zhoma, JX Tao, SY Huang RE McCullough, RG McCullough, CS Reeves, JT Reeves, LG Moore. Higher ventilatory drives in Tibetan than Han male residents of Lhasa. Am Rev Resp Dis (Suppl) 137:410, 1988.

Sun S, JG Zhang, ZX Zhoma, JX Tao, SY Huang, RE McCullough, RG McCullough, CS Reeves, JT Reeves, LG Moore. Higher exercise capacities in Tibetan than Han male residents of Lhasa (3658 m). FASEB J 2:A1281, 1988.

Sun SF, ZX Zhoma, JG Zhang, JX Tao, SY Huang, RG McCullough, RE McCullough, CS Reeves, JT Reeves, JT Reeves, LG Moore. Greater maximal 02 uptakes and vital capacities in Tibetan than Han male residents of Lhasa, 3658 M. Resp Physiol 79:151-162, 1990.

Moore LG. High altitude populations: Overview. In: Hypoxia: The Adaptations. JR Sutton, G Coates, J Remmers (eds). Philadelphia, BC Decker Inc, pp 50-52, 1990.

Moore LG and SF Sun. Physiological adaptation to hypoxia in Tibetan and acclimatized Han residents of Lhasa (3658 M). In: Hypoxia: The Adaptations. JR Sutton, G Coates, J Remmers (eds). Philadelphia, BC Decker, Inc, pp 66-71, 1990.

Huang SY, SF Sun, TS Droma, JG Zhuang, JX Tao, RG McCullough, RE McCullough, AJ Micco, JT Reeves and LG Moore. Internal carotid arterial flow velocity during exercise in Tibetan and Han residents of Lhasa (3658 m). Submitted, J Appl Physiol, 1991.

American Rev Resp Dis 137(suppl): 410, 1988

HIGHER VENTILATORY DRIVES IN TIBETAN THAN MALE RESIDENTS OF LHASA (3658 M). Drs. Shinfu Sun, Jian-Guo Zhang, Zhoma, and Tao, Tibetan Institute of Medical Research; Shao-Yung Huang, Shanghai Institute of Physiology; Robert E. McCullough, Rosann G. McCullough, Carol S. Reeves, John T. Reeves and Lorna G. Moore. CVP Research Laboratory, University of Colorado Health Sciences Center, Denver, Colorado.

The long residence of the Tibetan population at high altitude may have allowed it to adapt to its environment. Although reduced ventilatory responses have been reported in some high altitude populations, Nepalese Sherpas (a population which may have migrated from Tibet) had hypoxic responses not different from Westerners (Hackett et al., JAP, 1980). However, the comparison of Sherpas and Westerners was conducted at low altitude and was flawed by differences in body size between the groups and by lack of altitude residence in Westerners. In the present study, we compared (mean ± sem) Tibetan and Han residents in Lhasa to avoid these drawbacks. Heights (165 ± 1.6 vs. 166 ± .7 cm), weights (53 ±1.8 vs. 56 ± .8 kg), age (23 ± .7 vs. 24 ± .8 yrs.) of 20 Hans and 16 Tibetans were not different. Hans had shorter duration of residence at 3658 M (8 ± 1 vs. 24 ± 1 yrs) than Tibetans. Han subjects had lower hypoxic ventilatory responses (A values of 72 ± 13 vs. 128 ± 11), lower hypercapnic responses (S values of .97 ± .11 vs. 1.67 ± .17) and lower ventilatory frequencies (14.4 ± .9 vs. 17.1 ± 1) than Tibetans. Resting ventilations, O_2 saturation by ear oximeter, and end tidal O_2 and CO_2 tensions were not different. The relative preservation of ventilatory responses to hypoxia and hypercapnia in Tibetan subjects despite their longer duration of Lhasa residences, may reflect favorable adaptations in a population with a long history of living at high altitude.

FASEB J 2: A 1281, 1988

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HIGHER EXERCISE CAPACITIES IN TIBETAN THAN HAN MALE RESIDENTS OF LHASA (3658 M) S. Sun, J.G. Zhang, Tao Zhouna, S.Y. Huang, R.E. McCullough, R.G. McCullough, C.S. Reeves, J.T. Reeves, L.G. Moore. Tibet Inst Med Sci, Shanghai Inst Physiol, Univ Colo Hlth Sci Ctr, Denver, CO 80262.

The long duration of high altitude residence may have permitted Tibetans to become better adapted than other persons high altitude. If so, Tibetans might have higher exercise capacities than Hans (Chinese) living at the same altitude. Studies were performed in 16 Tibetan lifelong Lhasa residents and 20 Hans who had resided in Lhasa for 8 ± 1 yrs of similar age (23 ± 1 yrs), height (165 ± 1 cm), weight (54 ± 1 kg) and occupation (physicians, students). The Tibetans achieved higher symptom-limited maximum workloads (177 ± 5 vs 155 ± 5 watts, p<.01). At maximum effort, the Tibetans had higher oxygen uptakes per kg of body weight (51 ± 1 vs 46 ± 1 cc/min STPD p<.01), higher minute ventilations (149 ± 6 vs 126 ± 4 L/min BTPS, p<.01), and higher tidal volumes (2.9 ± 0.1 vs 2.4 ± 0.1 L BTPS, p<.01) than the Hans. Similarly high heart rates in the two groups (191 ± 3 vs 187 ± 3 beats/min) supported that maximal effort had been achieved. Resting vital capacity (5.1 ± 0.1 vs 4.3 ± 0.1 L BTPS, p<.01) and chest circumference (85 ± 1 vs 82 ± 1 cm, p<.05) were greater in Tibetans. Larger lung capacity may have permitted greater exercise ventilation and performance in the Tibetan than in the Han residents of Lhasa. Whether larger lungs resulted from a genetic trait or lifelong residence at high altitude was not studied.

Respiration Physiology, 79 (1990) 151–162
Elsevier

RESP 01616

Greater maximal O_2 uptakes and vital capacities in Tibetan than Han residents of Lhasa

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(Accepted for publication 14 October 1989)

Abstract. Maximal O_2 uptake provides an index of the integrated functioning of the O_2 transport system. Whether lifelong high altitude residents have greater maximal exercise capacities than acclimatized newcomers is of interest for determining whether years to generations of high altitude exposure influence maximal O_2 uptake and, if so, what components of O_2 transport are involved. We studied 16 Tibetan lifelong residents of Lhasa, Tibet, China (3658 m) and 20 Han ("Chinese") 8 ± 1 year residents of the same altitude who were matched for age, height, weight and lack of exercise training. At maximal effort, the Tibetans compared to the Hans had greater O_2 uptakes (51 ± 1 *vs* 46 ± 1 ml STPD · min^{-1} · $(kg\ bw)^{-1}$, $P < 0.05$), exercise workloads (177 ± 5 *vs* 155 ± 6 watts, $P < 0.05$), minute ventilations (149 ± 6 *vs* 126 ± 4 IBTPS/min, $P < 0.01$) and O_2 pulse (15.2 ± 0.4 *vs* 13.3 ± 0.5 ml O_2 consumption/heart beat, $P < 0.05$). Equally high heart rates were present at maximal effort (191 ± 3 *vs* 187 ± 3 beats/min, P = NS), supporting the likelihood that true maxima were achieved in both groups. The greater minute ventilation in the Tibetans resulted from greater tidal volume and the greater maximal tidal volume correlated positively with the resting vital capacity. We concluded that the Tibetans achieved a higher maximal O_2 uptake than the Hans, implying an increased capacity for O_2 transport to the working muscle.

Altitude, Exercise, Hypoxia, Ventilation; Maximal O_2 consumption

Maximal O_2 uptake decreases with acute ascent to high altitude, indicating a decrement in the integrated functioning of the O_2 transport system. This is not reversed over days to weeks of high altitude exposure but it is uncertain whether maximal O_2 uptake increases with years to generations of high altitude exposure and, if so, by what mechanisms and what components of O_2 transport are involved. One source of variability has been the extent of exercise training among the groups being compared.

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Lifelong high altitude residents have been reported to have greater maximal O_2 uptakes when compared to untrained, acclimatized newcomers but similar values when compared with well-trained athletes (Frisancho *et al.*, 1973; Grover *et al.*, 1967; Kollias *et al.*, 1968; Mazess *et al.*, 1969b). Unknown for these comparisons has been the extent of training in the lifelong high altitude residents. Additional sources of variability in these studies have stemmed from differences in body size between the lifelong residents and acclimatized newcomers as well as variation in the duration of altitude residence for the newcomers (Frisancho *et al.*, 1973; Mazess *et al.*, 1969b; Pugh *et al.*, 1964; Vogel *et al.*, 1974).

Our approach was to measure maximal exercise capacities in well-matched samples of lifelong high altitude residents and acclimatized newcomers. We selected Lhasa, Tibet Autonomous Region, China (3658 m) as the study site, given the availability of lifelong high altitude residents (Tibetans) and acclimatized newcomers (Han 'Chinese'). Of additional interest was the determination of maximal exercise capacity in Tibetans, given the likelihood that Tibetans have lived at high altitude longer than other high altitude residents (Denell *et al.*, 1988) and the absence of previous studies of exercise performance in Tibetans. Because the Tibetans were different from the Hans both with regard to their genetic background and altitude of birth, we would not be able to determine whether genetic or developmental influences were responsible for maximal O_2 uptakes differences observed. We would however be able to provide insight as to presence and magnitude of benefit in maximum O_2 transport available to the Tibetan high altitude native.

Methods

Subjects were 16 Tibetan and 20 Han male residents of Lhasa, Tibet Autonomous Region, China (3658 m, P_B 490 mm Hg) who granted informed consent to study procedures approved by the Human Research Committee of the University of Colorado Health Sciences Center. Hans comprise the majority ethnic group of China and are regarded as Chinese by Westerners. The Hans had been born at or near sea level in lowland China and all but two had migrated to Tibet after the age of 8. The Tibetans were born and had always lived at or above 3658 m and were of Tibetan descent without a known low altitude progenitor. Subjects were chosen randomly from volunteers 20–30 yr of age who had been judged healthy by history, physical exam, resting electrocardiogram and chest fluoroscopy. The majority were students, technicians or clerical workers. Although subjects in both groups routinely used bicycles for transportation, no subject was a trained athlete and none undertook exercise training or regular, strenuous exercise. Approximately half the subjects smoked cigarettes (6/16 Tibetans and 9/20 Hans) but the average number of pack years (packs/da*yr smoked) did not differ in the two groups (0.8 ± 0.3 *vs* 2.1 ± 0.7 pack yr, respectively, P = NS). Percent body fat as estimated from calculations based on the summed triceps, subscapular and

suprailiac skinfolds (Durnin and Womersley, 1974; Weiner and Lourie, 1981) was 9.6% in both groups.

Forced vital capacity and chest circumference was measured in triplicate using a mechanical spirometer (8-L Survey Spirometer, Warren Collins, Braintree, MA) and the highest value accepted. Chest circumference was measured at the junction of the 4th rib with the sternum with the subject at functional residual volume (Weiner and Lourie, 1981). Exercise was performed on a Monark cycle ergometer (model 868, Stockholm, Sweden) at 60 rpm in time to an audible metronome. Pedal revolutions counted electronically and the pedal resistance setting in kiloponds were used to calculate exercise workload in watts (Astrand and Rodahl, 1977). While the subjects breathed through a low resistance valve (Koegel, San Antonio, TX), samples of mixed expired air were collected in a 200 L meteorological balloon for subsequent measurement of fractional O_2 and CO_2 concentration using a fuel cell O_2 analyzer (model 101, Applied Technical Products, Denver, CO) and an infrared CO_2 analyzer (model LB-2, Sensor-Medics, Anaheim, CA). The analyzers were calibrated prior to each measurement of the expired air using ambient air and gas mixtures analyzed by the micro-Scholander technique on site. Mixed expiratory volume was measured using a Parkinson-Cowan ventilation meter previously calibrated against a Tissot spirometer after adjusting for the gas volume lost by O_2 and CO_2 sampling. Arterial O_2 saturation was monitored by an ear oximeter (model 47201A Hewlett Packard, Waltham, MA) and respiratory frequency by placing the ventilation meter on the inspiratory limb of the breathing circuit. Electrical signals from the ventilation meter, ear oximeter, O_2 and CO_2 analyzers were recorded on a a 4-channel recorder (model R304, Prime Line, San Francisco, CA). The electrocardiogram was obtained at rest and during each 30 sec of exercise (model 500 Viso-Cardiette, Sanborn, Waltham, MA). Hemoglobin was measured in resting subjects in duplicate from blood samples obtained without squeezing by finger stick using a photometer (Hemo-Cue, Aktiebolaget Leo, Helsingburg, Sweden) which had been calibrated with samples analyzed spectrophotometrically (Beckman model 34, Anaheim, CA) using the cyanmethemoglobin technique. In 49 comparisons, microhematocrit (x) was closely related to the hemoglobin measured simultaneously with the photometer (y) ($y = 0.28x + 2.8$, $r = 0.96$, $P < 0.0001$).

Subjects reported to the Tibet Institute of Medical Sciences in Lhasa after having fasted for at least one hour. Forced vital capacity and chest circumference were measured in subjects while standing. Resting ventilation and O_2 uptake were measured after the subject had been seated in a chair at rest for at least 20 min. The subject then performed cycle exercise at 30 watts for 5 min with ventilation and O_2 uptake measurements being made during the last 2 min. After resting for at least 5 min, the subject cycled for 4 min at approximately 90 watts and the measurements were repeated during the final 1 to 1.5 min of the exercise. After an at least 10 min rest, the measurements were repeated at an exercise level of 140 to 150 watts. Subsequent bouts of exercises were performed at higher workloads until the subject reached a plateau in O_2 uptake as previously described (Moore *et al.*, 1986), the subject could not complete the 3 min

exercise period or refused a higher workload. The heart rates in the 9 subjects achieving a plateau in O_2 uptake were not different from those in the 26 subjects with symptom-limited maxima (190 ± 5 beats/min *vs* 188 ± 2 beats/min, P = NS).

Statistics. Mean values ± 1 standard error of the mean (SEM) are reported in the text, tables, and figures. Comparisons between Tibetan and Han subjects were performed using two sample (Students) *t*-tests. Linear regression analysis and correlation coefficients were used to assess relationship between variables. Differences between samples and relationships between variables were considered significant when $P < 0.05$.

Results

The Han and Tibetan subjects were similar in age, height, weight, and hemoglobin concentration but, as a result of the study design, the Tibetans had lived at high altitude longer than the Hans (table 1). The Tibetans compared to the Hans had greater vital capacity and chest circumference and chest circumference (y, cm) was related to vital capacity (x, ml_{BTPS}) among all subjects ($y = 0.0042x + 63.8$, $P < 0.01$).

At rest, Tibetans had a higher minute ventilation and respiratory frequency but heart rate, arterial O_2 saturation, and O_2 consumption were not different in the two groups (table 2). During submaximal exercise at mild workloads (30 and 88–89 watts), ventilation, heart rate and O_2 uptake were similar in the Tibetan and Han groups. At moderate exercise (141–147 watts), the Tibetans compared to the Hans had a higher tidal volume, lower respiratory frequency but similar minute ventilation, heart rate and O_2 consumption (table 2).

At maximal effort, the Tibetan subjects had higher maximal O_2 uptakes and achieved higher maximal workloads than the Han subjects. Higher maximal O_2 uptakes were present in the Tibetan compared to the Han group whether O_2 uptake was expressed as the total O_2 uptake or per kg body weight (table 3). The Tibetans also had higher maximal O_2 uptakes when only the 4 Tibetans and the 5 Hans achieving a plateau in

TABLE 1

Subject characteristics (mean ± SEM).

Variable	Tibetan (N = 16)	Han (N = 20)	*P*
Age, yr	24 ± 1	23 ± 1	NS
Height, cm	166 ± 1	165 ± 2	NS
Weight, kg	56 ± 1	54 ± 2	NS
Hemoglobin, gm/100 ml	18.1 ± 0.3	18.4 ± 0.2	NS
Years residence ≥ 3658 m	24 ± 1	8 ± 1	<0.01
Forced vital capacity ml BTPS	5080 ± 125	4280 ± 143	<0.01
Chest circumference, cm	85.0 ± 0.7	80.9 ± 0.8	<0.01

O_2 uptake were compared (53 ± 2 *vs* 47 ± 2 ml/min/kg body weight, $P < 0.05$). Minute ventilation at maximal effort was greater in the Tibetans than the Hans due to increased tidal volume (table 3) and tidal volume at maximal effort correlated with the maximum O_2 uptake normalized for body size among all subjects (fig. 1). The tidal volume at

TABLE 2

Measurements (mean ± SEM) at rest and during submaximal exercise.

Workload	Group	HR	Sa_{O_2}	$\dot{V}_E$	f	V_T	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$
0	Tibetan	72	90.5	11.6	17.1	0.72	276	228
		±4	±0.5	±0.5*	±1.0*	±.06	±14	±12*
0	Han	74	90.6	10.0	14.4	0.77	256	194
		±3	±0.5	±0.5	±0.9	±.07	±14	±10
30	Tibetan	102	90.0	32.3	24.7	1.32	808	753
		±4	±0.3	±1.0	±0.9	±.03	±24	±18
30	Han	108	89.4	32.6	24.9	1.37	862	729
		±3	±0.5	±1.4	±1.4	±.09	±29	±14
89	Tibetan	137	87.1	54.5	29.0	1.92	1603	1471
		±5	±0.6	±1.9	±1.4	±.10	±30	±35
88	Han	144	86.5	56.9	32.1	1.81	1583	1463
		±4	±0.8	±1.3	±1.2	±.07	±30	±17
147	Tibetan	174	85.9	95.2	37.8	2.53	2363	2409
		±4	±0.7	±2.7	±1.3*	±.06*	±34	±39
141	Han	174	83.2	95.1	40.9	2.36	2355	2304
		±4	±1.2	±4.6	±2.1	±.12	±55	±42

Abbreviations: HR = heart rate (beats/min), Sa_{O_2} = arterial O_2 saturation (%), $\dot{V}_E$ = ventilation (1 BTPS/min), f = respiratory frequency (breaths/min), V_T = tidal volume (1 BTPS), $\dot{V}_{O_2}$ = O_2 consumption (ml STPD/min), $\dot{V}_{CO_2}$ = CO_2 production (ml STPD/min). * = comparisons of Tibetans and Hans, $P < 0.05$.

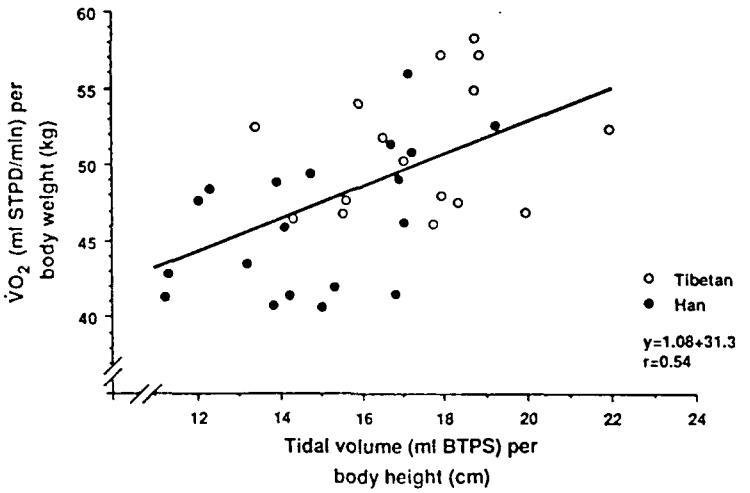

Fig. 1. Tidal volume per cm body height correlates with the maximal O_2 uptake (VO_2) per kg body weight among all subjects.

TABLE 3

Measurements at maximal exercise.

Id No.	Watts	HR	Sa_{O_2}	$\dot{V}_E$	V_T	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	$\dot{V}_{O_2}$/kg	O_2 Pulse
Tibetan									
19	206	178	79.0	192	3.68	2937	3114	52.4	16.5
37	165	203	86.0	148	2.85	2864	2838	46.2	14.1
45	192	185	80.0	164	3.22	3209	3596	57.3	17.3
52	173	210	65.0	128	2.81	2959	2894	51.9	14.1
53	204	178	85.5	113	2.82	2868	2984	50.3	16.1
54	199	195	88.0	159	3.05	3082	3245	55.0	15.8
55	177	200	84.5	130	2.51	2482	2445	46.8	12.4
56	159	202	87.8	151	2.96	2498	2441	48.0	12.4
57	198	185	88.5	175	3.02	3321	3027	57.3	18.0
58	191	199	85.5	179	3.47	3094	3164	46.9	15.5
59	171	210	87.0	144	3.01	2715	2716	47.6	12.9
60	128	180	85.0	112	2.34	2559	2693	46.5	14.2
61	187	185	85.0	168	3.09	3096	2719	58.4	16.7
62	152	175	89.0	123	2.61	2576	2670	47.7	14.7
63	151	183	82.0	137	2.21	2837	2767	52.5	15.5
64	183	190	82.0	162	2.60	3085	3169	54.1	16.2
Mean	177*	191	83.7	149*	2.89*	2886*	2905*	51.8*	15.2*
SEM	5	5	1.5	6	0.10	65	77	1.1	0.4
Han									
16	147	164	87.0	125	2.49	2560	2313	42.0	15.6
20	146	183	85.0	157	2.97	3002	2345	50.9	16.4
31	157	188	91.0	110	2.89	2284	2485	40.8	12.1
33	169	197	82.5	136	2.39	2656	2616	–	13.5
38	98	176	85.5	105	2.34	2076	2242	41.5	11.8
39	174	196	81.5	156	2.99	3290	2984	46.3	16.8
40	177	179	85.0	124	2.88	2871	2672	41.6	16.0
44	152	188	81.0	110	1.96	2148	2452	47.7	11.4
46	133	199	83.0	106	2.15	1955	2183	46.0	9.8
47	171	185	84.0	126	3.14	2637	2805	52.7	14.3
48	118	160	87.5	106	1.83	2030	2292	41.4	12.7
49	114	193	89.0	99	1.79	1673	1902	42.9	8.7
50	164	202	82.0	124	2.68	2524	2529	51.5	12.5
51	180	189	82.0	144	2.32	2397	2552	43.6	12.7
66	173	213	82.0	134	2.69	2916	2681	56.1	13.7
67	152	194	84.5	113	2.35	2377	2419	49.5	12.3
68	177	181	84.0	144	2.33	2837	2884	48.9	15.7
69	179	183	81.5	151	2.91	2894	2860	49.1	15.8
70	183	197	71.0	104	2.00	2427	2711	48.5	12.3
71	135	176	89.5	123	2.16	1919	2231	40.8	10.9
Mean	155	187	83.9	125	2.46	2474	2508*	46.4	13.3
SEM	6	3	0.9	4	0.09	95	62	1.1	0.5

Abbreviations: see Table 2, O_2 pulse = ml O_2 consumption/heart beat. *$P < 0.05$.

maximal effort also correlated with the vital capacity (fig. 2) and chest circumference ($r = 0.42$, $P < 0.05$) measured at rest. Arterial O_2 saturation at maximal effort was similar in the Tibetan and Han subjects (table 3). The relationship between arterial O_2 saturation and O_2 consumption across the full range of submaximal and maximal workloads was similar in the two groups but the Tibetans tended to have a lower slope ($P = 0.08$), indicating a trend toward a higher arterial O_2 saturation for a given level of O_2 uptake in the Tibetans compared to the Hans (fig. 3). Maximal heart rate was not different in the two groups but, since the Tibetans had a higher maximal O_2 uptake, the

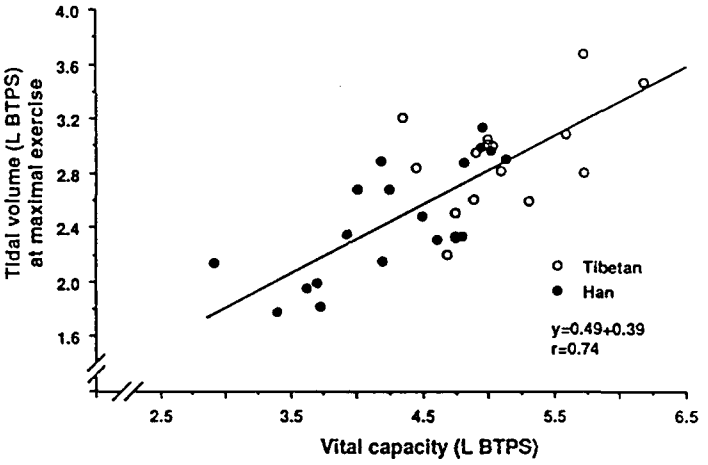

Fig. 2. Vital capacity measured at rest correlates with tidal volume at maximal exercise among Han and Tibetan subjects.

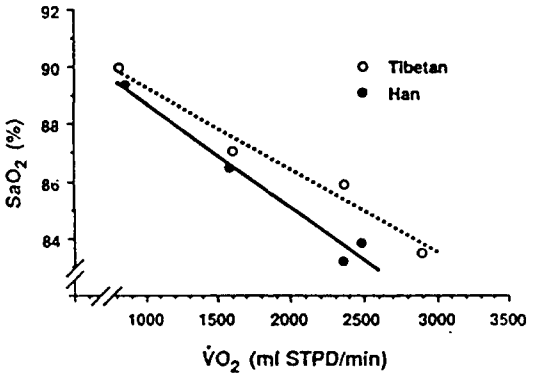

Fig. 3. The relationship between arterial O_2 saturation and O_2 consumption across the full range of submaximal and maximal workloads was similar in the two groups but the Tibetans tended to have a lower slope, implying a higher arterial O_2 saturation (Sa_{O_2}) for a given level of O_2 consumption ($\dot{V}_{O_2}$) than the Han subjects (Tibetans: $y = -0.0029x + 92.2$; Hans: $y = -0.0037x + 92.5$; comparison of slopes, $P = 0.08$).

O_2 pulse (O_2 consumption per heart beat) was greater in the Tibetan than the Han group (table 3). Among all subjects, the O_2 pulse correlated positively with the maximal exercise workload (fig. 4).

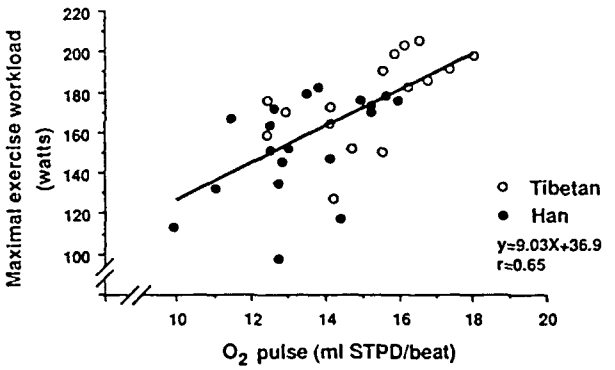

Fig. 4. The maximal exercise workload is correlated with the O_2 pulse at maximum effort among all subjects.

Discussion

This study found that Tibetan lifelong residents of Lhasa (3758 m) had higher maximal O_2 uptakes than Han ('Chinese') acclimatized newcomers. By subject selection, the Tibetan and Han groups were similar in age, body size, smoking history and sedentary occupation with no subject engaged in exercise training. Therefore we considered it unlikely that the differences in maximal O_2 uptake resulted from poor matching of study groups. In support of the higher maximal O_2 uptakes observed in the Tibetan compared to the Han subjects were the higher maximal workloads achieved by the Tibetans. That the group differences were not likely due to the closer attainment of a true maximum in the Tibetans was supported by finding higher maximal O_2 uptakes in the subset of Tibetans whose maximal O_2 uptake was defined by achieving a plateau in O_2 consumption. The high heart rates by sea level standards (Astrand and Rodahl, 1977), equally high heart rates at maximal effort in both groups and the absence of heart rate differences between subjects achieving a plateau in O_2 uptake *vs* those with symptom-limited maxima further supported the likelihood that all subjects were near or at maximal effort. We concluded that the higher maximal O_2 uptakes measured in the Tibetans were real and implied a greater maximal O_2 transport to the working muscle in the Tibetan compared to the Han subjects. This is not to imply that all Tibetans or high altitude natives have maximal O_2 uptakes that exceed those of all Hans or acclimatized newcomers, given the existence of normal, intersubject variability in any population. It does imply, however, that when the level of exercise training, body size and other factors are controlled to the extent possible, Tibetan high altitude natives have a small (12%) but significantly greater O_2 transport capacity than acclimatized Han

newcomers. Thus, the present study agreed with previous reports of an increased maximal O_2 uptake in native high altitude residents when compared with untrained, acclimatized newcomers but disagreed with the results of comparisons between lifelong high altitude residents and trained newcomers (Frisancho *et al.*, 1973; Grover *et al.*, 1967; Kollias *et al.*, 1968; Mazess *et al.*, 1969a,b).

A greater maximal O_2 transport to the working muscles could have been due to improved performance of one of more components of the O_2 transport system. While only limited information was obtained in the present study, we examined the data available to assess which of four possible components of the O_2 transport system may have been involved: (1) increased alveolar ventilation, (2) greater alveolar-arterial O_2 diffusion, (3) higher circulatory O_2 transport, and (4) increased tissue O_2 extraction.

Concerning the first possibility, greater minute ventilation was observed at maximal effort in the Tibetan compared to the Han subjects. Since ventilation was the same at a given level of O_2 uptake, it appeared that the Tibetans did not have an increased alveolar ventilation per unit metabolic rate (hyperventilation). Rather, the Tibetans achieved a greater minute ventilation at maximal effort due to an increased tidal volume. That the greater tidal volume correlated with the vital capacity and represented the same fraction of vital capacity in both groups (0.571 ± 0.17 *vs* 0.572 ± 0.015, respectively, P = NS) suggested that a larger vital capacity permitted the Tibetans to attain a greater maximal tidal volume and ventilation. One problem with this interpretation is that minute ventilation is not usually considered to limit maximal O_2 uptake since an increase in ventilation can occur at maximal effort without an increase in O_2 consumption (Grover *et al.*, 1967). However, in the setting of a larger lung volume, an increase in minute ventilation can be achieved without raising respiratory frequency and thus avoid the potentially exercise-limiting symptoms of dyspnea (Balke, 1964). In addition, under conditions of greater lung O_2 diffusing capacity, increased ventilation could raise arterial oxygenation.

Concerning the second possibility, alveolar-arterial O_2 diffusion was not measured but the data obtained was consistent with the possibility of an increased lung volume and diffusing capacity among the Tibetans. An increased lung volume was suggested by the greater resting vital capacities and chest circumferences of the Tibetan compared to the Han subjects. It has been reported that chest depths and width dimensions of Tibetan residents of Nepal were less than Andean natives' (Beall, 1982), leading to the suggestion that lung volume was not increased in Tibetan high altitude residents. However, other studies have found chest circumference and vital capacities in Tibetans and Himalayan residents more generally to be at least as great as in other high altitude residents and to be clearly greater in relation to body size than in low altitude residents (Hackett *et al.*, 1980; Kennter, 1969; Malik and Singh, 1978; Sloan and Masali, 1978). An increased lung volume has been shown to be accompanied by an increased pulmonary diffusing capacity in previous studies at high altitude (Cerny *et al.*, 1973; DeGraff *et al.*, 1970; Dempsey *et al.*, 1971; Guleria *et al.*, 1971; Johnson *et al.*, 1985) and lung O_2 diffusion may limit O_2 transfer particularly at high altitude (West *et al.*, 1983). The possibility of an increased lung diffusing capacity was supported by the trend

toward higher arterial O_2 saturation at a given level of O_2 uptake in the Tibetan compared to the Han subjects (fig. 3). Needed however are direct measurements of lung volume, diffusing capacity and alveolar-arterial O_2 gradients in Tibetan and Han subjects.

Concerning the third and fourth possibilities, the greater O_2 pulse in the Tibetans than Hans indicated a larger amount of O_2 consumed per heart beat which may, in turn, have been due to an increased circulatory O_2 transport (arterial O_2 content * cardiac output) or to a greater tissue O_2 extraction. Since arterial O_2 saturation was similar in the two groups at maximal effort and if hemoglobin concentration did not differ (resting values were not different), arterial O_2 content was likely to be similar in the two groups. Therefore, either increased stroke volume acting to raise cardiac output, blood flow redistribution to favor the exercising limbs or greater tissue O_2 extraction was likely to have been responsible for increasing O_2 pulse in the Tibetan compared to the Han subjects. The possibility of an increased stroke volume and cardiac output during exercise in lifelong high altitude residents compared to acclimatized newcomers is supported by previous studies in Andean natives and in one Sherpa high altitude resident (Pugh *et al.*, 1964; Vogel *et al.*, 1974).

In conclusion, higher maximal O_2 uptakes among Tibetan high altitude natives than acclimatized Han newcomers implies an increased capacity for O_2 supply and/or O_2 extraction by the working muscle. Problems inherent in previous comparisons of maximal O_2 uptake in lifelong high altitude residents and acclimatized newcomers were overcome in the present report by matching of study groups with regard to the extent of exercise training and body size. Our findings were consistent with the possibility that larger lungs permitted the Tibetans to achieve a greater exercise ventilation and, perhaps by enhancing lung diffusing capacity, tended to raise arterial O_2 saturation. Other factors including greater stroke volume and tissue O_2 extraction may also have contributed to better exercise capacity in Tibetan than Hans residents of 3658 m. Since the Tibetan and Han subjects differed both in terms of their altitude of birth and duration of high altitude exposure, the present study was not informative about whether genetic or developmental influences were involved in the maximal O_2 uptake differences observed. Future studies are needed to identify the components of O_2 transport responsible for raising maximal O_2 uptakes in the Tibetan subjects and to determine whether differences in exercise capacity likely stemmed from genetic factors or developmental influences.

Acknowledgements. The enthusiastic cooperation of the volunteer subjects and the extensive cooperation from Dr Tse Ren Zhou Ga and Dr Tuedeng of the Tibet Autonomous Region Ministry of Health, Dr Fung of the Provincial Hospital, and W-H Zhang and Y-Z Pong made this study possible. Additional assistance was provided by Ms Debbie Gallantine, Lt Col Hambree, Mr Dave Hucksel, Dr Shu-Tsu Hu, Dr Charles Irwin, Ms Nancy Mohler, Mr Dan Nelson, Mr Bob Owens, Mr Chuck Rybar for their help in the planning and logistical arrangements for the study. Dr Robert F. Grover, Mr William Moore, and Dr Garrison Rapmund provided advice and encouragement throughout. Finally we wish to thank without whom the study would not have been possible. This research was supported by U.S. Army Contract No DAMD 17-87-C-7202, an RCDA NIH-CHD 00681 to L.G. Moore and NIH Grant HL-14895.

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9 HIGH ALTITUDE POPULATIONS: OVERVIEW

LORNA GRINDLAY MOORE

Populations live permanently at high altitude on each of the major continents of the world: North and South America, Asia, and Africa. Yet the earliest and still the majority of high altitude studies are performed on newcomers after short periods of high altitude sojourn. As a result, our understanding of physiologic responses to high altitude is far better for the first minutes to days than for periods of years to generations of high altitude exposure. An understanding of the effects of longer duration of high altitude exposure is important, in general, to determine whether adaptation to high altitude in the Darwinian sense has occurred and, in particular, to determine the genetic and physiologic mechanisms involved in such long-term processes.[8] In addition, because populations are comprised of people of both genders, of all ages, and with the full range of disease conditions affecting oxygen supply (e.g., heart, lung, or blood disorders) or oxygen demand (e.g., pregnancy and exercise), studies of populations living permanently at high altitude can help to inform us as to whether the effects of high altitude are the same for all people or whether gender, age, health status, and other conditions influence the observed physiologic responses to high altitude.

The first systematic study of permanent residents at high altitude was carried out by a remarkable 35-year-old woman, Mabel Purefoy Fitzgerald.[9] She came to Colorado from Oxford, England, in 1911 as a member of the illustrious Anglo-American Pike's Peak Expedition of that same year. She was not, however, permitted to join Drs. J. S. Haldane, C. Gordon Douglas, Yandell Henderson and Edward C. Schneider on the summit of Pike's Peak. Life atop the peak was considered too rigorous and inappropriate for a young woman. Undaunted, she loaded up pack animals with her Haldane apparatus and other necessary research supplies and set off to study large numbers of men and women residing permanently under the truly arduous conditions of the Tom Boy Mine, Camp Bird Mine, Portland Mine, and other high altitude locales

> ... for the purpose of determining the changes in the alveolar air and the percentage of hemoglobin in the blood of persons residing permanently at such heights.[9(p351)]

She and the scientists atop Pike's Peak shared the goal of determining whether high altitude residence prompted sustained alveolar hyperventilation and thus served to lower alveolar PCO_2 and raise PO_2. But she chose to investigate this phenomenon by describing the relationship between alveolar PCO_2 and alveolar PO_2 in both genders across a wide range of altitudes. Our modern concept of ventilatory acclimatization can be traced back to this expedition and in particular, to her pioneering measurements. She was fully aware of the value of undertaking such studies in high altitude populations:

> Until now, the observations on the changes in the alveolar air and hemoglobin at high altitudes have been practically confined to the various observers and their companions, who were making but a short stay at various heights, and no systematic work has been done on residents, or over a wider range of altitude. For such work, Colorado is eminently suitable, as not only are there several readily accessible towns situated at a high altitude, but mines, at which the miners both work and live, are to be found up to the height of 13,000 ft.[9(p351)]

Little further study was undertaken concerning time-dependent physiologic processes over longer periods of high altitude exposure. Nonetheless, Joseph Barcroft concluded in 1925 that

> the acclimatized man is not the man who has attained to bodily and mental powers as great in Cerro De Pasco as he would have in Cambridge (whether that town be situated in Massachusetts or in England). Such a man does not exist. All dwellers at high altitudes are persons of impaired physical and mental powers.[1(p176)]

South American investigators, most notably Alberto Hurtado and Dr. Carlos Monge, challenged Barcroft's view. Hurtado pointed to the enlarged chest and lung dimensions of the high altitude native, smaller body size and slowed body growth as possible developmental or genetic adaptations for permanent high altitude residence.[15] Carlos Monge wrote an important monograph in which he pointed out that large numbers resided permanently in Cerro de Pasco and throughout the Andean region and had done so successfully for millennia.[22] This contradicted the conclusion that the high altitude dweller was un-

adapted or maladapted. In an earlier, Spanish version of the monograph,[21] Carlos Monge speculated as to the possible source of Barcroft's failure to recognize the possibility of physiologic adaptation among permanent high altitude residents:

> The investigator who contemplates the study of acute hypoxia has a different mental attitude than that required for the study of high altitude residents. In the first case, we deal with a stress which must be immediately compensated for in linear relation to the ambient oxygen tension . . . In the second case, we deal with a being in whom the wisdom of homeostasis has organized a new physiological system.[21(p5)] [author's translation]

The search for a "new physiological system" was begun more intensively in the 1960s and 1970s with studies of high altitude residents of the Andean, Rocky Mountain and Himalayan regions. A partial list of these studies is included in Figure 9-1. The largest number of studies were conducted in Andean countries concerning characteristics of ventilation, ventilatory control, circulatory oxygen transport, exercise performance, chest and lung dimensions, and body growth. Many of these were carried out under the auspices of the International Biological Program. A smaller but still considerable number of investigations carried out in high altitude residents of Colorado addressed effects of years (but not generations) of high altitude exposure on characteristics of exercise performance, gas exchange and the control of breathing. Surprisingly few, if any, comparisons were made between these two high altitude regions; for the most part, different disciplines and investigative teams worked in the two areas. In addition, very little was known during this period about the high altitude residents of the Himalayan region (see Fig. 9-1).

The series of papers in this symposium represent several new investigations being undertaken in Andean and Himalayan high altitude residents. That several such projects are actively underway prompted the present symposium, the purpose of which is to provide a forum to exchange information among persons conducting such studies and to disseminate the information to interested scientists.

<u>Rocky Mountains</u>

1967 Grover - exercise performance
1970 DeGraff - diffusing capacity
1971 Weil - control of breathing
1971 Dempsey - gas exchange
1978 Kryger - CMS

<u>Himalayas</u>

1965 Lahiri - exercise, ventilation
1980 Hackett - control of breathing
1981 Hu, Huang - ventilation
1984 Beall - hemoglobin

<u>South America</u>

1932 Hurtado - ventilation
1957 Chiodi - ventilation
1968 Sorensen - control of breathing
1968 Kollias - exercise performance
1969 Mazess - exercise performance
1969 Frisancho - growth
1974 Vogel - cardiac output
1964-1974 - International Biological Program

Figure 9-1 A representative list of publications from studies of high altitude during the 1950–1980 period. See References for a complete listing for each study.

At least three issues are common to the following four chapters. The first issue concerns the meaning of the term "adaptation." Adaptation in the Darwinian sense refers to the ability to live and reproduce successfully in a given environment.[8] Yet often, the term is used to refer simply to the presence of a trait that is presumed to benefit the organism; rarely do we know whether or not actual benefit exists. Even if benefit can be demonstrated, it is not clear whether the adaptation merely reflects current utility or whether the adaptation was the product of natural selection for the particular attribute in question. Also unknown is whether the mechanisms responsible for the adaptation are part of the generalized phenotypic plasticity present in all members of the human species, are developmental in origin and hence acquired through the process of growth and development, or are under genetic control.

A second issue concerns the involvement of components of the oxygen transport system. The oxygen transport system (Fig. 9-2) can be viewed as being comprised of two active pumps, the lungs and the heart, and two passive diffusion steps. The lungs transfer oxygen from the atmosphere to the alveoli where diffusion serves to transfer the oxygen across the alveolar–arterial membrane. Oxygen enters the bloodstream and is pumped by the heart throughout the circulation. A final diffusion step is required to transfer oxygen from the tissue capillaries to the cell mitochondria in order for oxidative metabolism to take place. Understanding the involvement of the oxy-

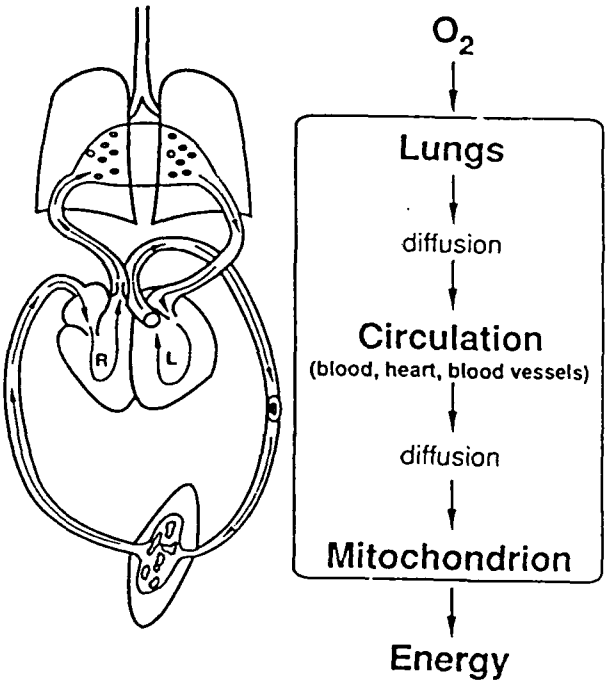

Figure 9-2 Oxygen transport system (adapted from Weibel[23]).

gen transport system in relation to the particular high altitude attribute (e.g., hemoglobin level, exercise performance, body growth, lactate concentration) is necessary in order to determine the mechanisms responsible and the adaptive significance for the attribute in question. Attaining such an understanding is becoming increasingly feasible, given the growing sophistication, accessibility and noninvasive nature of research techniques available.

The third issue stems from recognizing the possibility of variation both within and between populations. Characterizing such variation by age, gender and geographic location as well as by health status may prove an important tool to uncover whether adaptive processes are the same or different in the various high altitude populations. In particular, the presentations in this section permit us, for the first time, to remedy deficiencies in our understanding of Himalayan residents and therefore, to begin to make comparisons among the Andean and Himalayan populations, the world's longest-occupied high altitude regions. In this fashion, we may in fact succeed in identifying the effects of years to generations of high altitude exposure and begin to understand the range of high altitude effects both within and between the world's various high altitude populations.

This symposium thus offers an exciting opportunity to examine the evidence available on physiologic responses to longer (years to generations) duration of high altitude exposure. The questions as to whether physiologic traits confer adaptive benefit, whether genetic factors influence the adaptive process and whether the course of high altitude adaptation is similar or different among long-resident high altitude populations are important but, as of the present, unresolved. At a time when an increasingly detailed understanding of the mechanisms underlying hypoxic responses is emerging from molecular and cell biology, comparative studies of high altitude populations promise to expand our view of hypoxic responses in other, more integrating but equally innovative dimensions.

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In Hypoxia: The Adaptations (Ed JR Sutton, G Coates, JE Rennes) Toronto: B C Dekker pp 66-71, 1991

12 PHYSIOLOGIC ADAPTATION TO HYPOXIA IN TIBETAN AND ACCLIMATIZED HAN RESIDENTS OF LHASA

LORNA GRINDLAY MOORE
SHIN-FU SUN

It is well known that time-dependent factors influence the physiologic responses to high altitude. For example, acclimatization occurs over hours to days of high altitude exposure to produce a rise in effective alveolar ventilation despite the inhibitory influences of hypocapnia and alkalosis. Whether changes in the physiologic responses to high altitude continue over years to generations is poorly understood. Difficulties in longitudinal study design are responsible, at least in part, for the absence of knowledge concerning the effects of long-term high altitude exposure. These difficulties stem, in turn, from the potentially confounding influences of advancing age on the effects of prolonged residence at high altitude and the practical problems of subject follow-up and long-term funding inherent in the conduct of longitudinal studies.

An approach to the identification of the effects of long duration of high altitude residence which has been frequently employed in South and North American studies is to compare physiologic characteristics of persons who are descended from long-resident high altitude populations with persons who have recently migrated from low to high altitude. The physiologic characteristic most commonly examined has been the maximal exercise capacity, since it provides an index of the integrated functioning of the oxygen transport system. Since maximal exercise capacity is clearly reduced by ascent to high altitude and remains below sea level values after acclimatization is completed,[4] comparisons of natives and acclimatized newcomers could be expected to reveal whether years to generations of high altitude exposure restore maximal exercise capacity to sea level values. However, the interpretation of study results has been difficult given the absence of well-controlled comparisons among the groups being considered. One difficulty has been the extent of exercise training. Maximal oxygen uptake has been shown to be similar in native and newcomer groups when the newcomers have been well-trained athletes, but greater in natives when the newcomers have been untrained.[10,11,15,17] Unknown in previous comparisons has been the extent of exercise training among the high altitude natives. Other difficulties have stemmed from differences in body size and percent lean body mass as well as duration of high altitude residence among the newcomer groups being considered.[15,16,19] Given that the natives and newcomers frequently differ with regard to both genetic background and altitude of birth, it has also proven difficult in previous studies to separate genetic from developmental influences on maximal exercise capacity. Finally, the absence of comparisons with well-matched groups living at sea level has prevented determining whether maximal exercise capacity of high altitude natives has been restored to sea level values.

The strategy that we employed to assess the effect of years to generations of high altitude exposure on maximal exercise capacity was to compare well-matched samples of young Tibetan men who were lifelong high altitude residents of Lhasa (elevation 3,658 m or higher) and descended from a long-resident high altitude popu-

lation with a non-native high altitude population consisting of Hans ("Chinese") who had migrated as adults from lowland China to Lhasa. The determination of whether Tibetan high altitude natives have greater maximal exercise capacity than Han acclimatized newcomers is of interest for several reasons. First, because the two samples could be matched for body size, health status and extent of exercise training, the comparison of Tibetans and Hans would avoid the problems of previous studies in which pronounced differences in training and body size characteristics prevented determining whether high altitude natives had an increased maximal exercise capacity. Second, previous studies in Tibetans have been limited to measurements of ventilation[13] and hemoglobin[3,27] and have not included assessment of maximal exercise capacity. Given the likelihood that Tibetan populations have lived longer at high altitude than populations elsewhere in the world,[7] measurements of maximal exercise capacity in Tibetans and Hans should be informative as to whether generations of high altitude exposure have resulted in changes in the oxygen transport system and improved exercise performance. However, the present study would not be able to determine whether differences in maximal exercise capacity were due to developmental or genetic factors, since the Tibetans and the Hans differed with regard to both their genetic background and their altitude of growth and development.

TECHNIQUES

Subjects for this report were 16 young Tibetan men and 20 young Han men residing in Lhasa, Tibet Autonomous Region, China (3,658 m, P_B 490 mm Hg). Studies were carried out September to October, 1987. The two groups of subjects were of similar age, height and weight (Table 12–1). To the extent possible, nonsmokers were chosen, but approximately half of each sample smoked a modest number of cigarettes. Of importance was that subjects were deliberately chosen so that none engaged in regular strenuous exercise or exercise training. The Tibetans were born and had always lived above 3,658 m and were of Tibetan descent without a known low altitude progenitor. The Hans were born at or near sea level in lowland China and had migrated to Tibet 8 ± 1 years previously (see Table 12–1).

Subjects were studied at rest and during progressive exercise up to and including maximal effort. Details pertaining to the study techniques have been published previously[21] and are therefore summarized only briefly here. Exercise was performed on a cycle ergometer, initially at 30 W for 5 min and subsequently at 90, 140–150 W and at increasingly higher workloads until the subject reached a plateau in oxygen uptake,[18] could not complete at least a 3 min exercise period, or refused a higher workload. While at rest and during each level of exercise, the subjects breathed through a low resistance valve. Samples of mixed expired air were collected and the volume was measured using a Parkinson-Cowan ventilation meter and analyzed for fractional oxygen and carbon dioxide concentration using well-calibrated oxygen and carbon dioxide gas analyzers (model 101, Applied Technical Products, Denver, CO) and an infrared CO_2 analyzer (model LB-2, Sensor-Medics, Anaheim, CA). Arterial O_2 saturation was monitored by ear oximetry (model 47201 A, Hewlett-Packard, Waltham, MA) and respiratory frequency by placing the ventilation meter on the inspiratory limb of the breathing circuit while recording the electrical signals on a four-channel recorder (model R304, Prime Line, San Francisco, CA). The electrocardiogram was recorded at rest and during each 30 seconds of exercise (model 500, Viso-Cardiette, Sanborn, Waltham, MA). Hemoglobin was measured in resting subjects in duplicate from blood samples obtained by finger stick without squeezing (Hemo-Cue Photometer,

TABLE 12–1 Subject Characteristics at Rest and During Maximal Exercise

	Tibetan (n = 16)	*Han (n = 20)*	*P Value*
Rest			
Age, yr	24 ± 1	23 ± 1	NS
Height, cm	166 ± 1	165 ± 1	NS
Weight, kg	56 ± 1	54 ± 2	NS
Years ≥ 3,658 m	24 ± 1	8 ± 1	<.01
Smoking, pack yr	0.8 ± 0.3	2.1 ± 0.7	NS
Arterial O_2 saturation, %	90.5 ± 0.5	90.6 ± 0.5	NS
Hemoglobin, g%	18.1 ± 0.3	18.4 ± 0.2	NS
Maximal exercise			
O_2 consumption, ml/kg	51.8 ± 1.1	46.4 ± 1.1	<.01
Workload, W	177 ± 5	155 ± 6	<.01
Ventilation, ml_{BTPS}/min	149 ± 6	125 ± 4	<.01
Arterial O_2 saturation, %	83.7 ± 1.5	83.9 ± 0.9	NS
Heart rate, bpm	191 ± 3	187 ± 3	NS
O_2 pulse, ml/beat	15.2 ± 0.4	13.3 ± 0.5	<.01

Aktiebolaget Leo, Helsingburg, Sweden). Forced vital capacity was measured in triplicate using a mechanical spirometer (8-L Survey Spirometer, Warren Collins, Braintree, MA) and the highest value accepted. Chest circumference was measured at the level of the junction of the fourth rib with the sternum with the subject at functional residual volume.[25] Percent body fat was calculated from triceps, subscapular and suprailiac skinfold measurements according to previously published algorithms.[8]

FINDINGS

Maximal Exercise Capacities

We found that Tibetan residents of Lhasa (3,658 m) had higher maximal exercise oxygen uptake than similarly aged Han ("Chinese") men (see Table 12–1). To determine whether the differences we observed were real, we examined possible sources of error stemming from measurement techniques, the extent of the subject's exercise training and his willingness to engage in maximal exercise. Since our gas analyzers were well calibrated in Lhasa against known gases and the ventilation meter had been calibrated against the Tissot spirometer, methodologic error in the measurement of oxygen uptake seemed unlikely. Further, our data on maximal exercise oxygen consumption were supported by the independently measured higher maximal workloads attained in the Tibetan compared to the Han subjects. Because the subjects were closely matched for age, body size, smoking history and sedentary occupation with no subject engaged in regular exercise or exercise training, the differences in maximal exercise capacity likely did not result from poor matching of study groups. Lean body mass, as estimated from measurements of percent body fat, was also identical in the two groups. The classic criterion for maximal oxygen uptake is the attainment of a plateau in oxygen consumption despite a rise in workload. While only five subjects met this criterion, their maximal heart rates were not different from those in the 31 subjects with symptom-limited maxima (191 ± 5 bpm versus 189 ± 2 bpm), which suggests that all subjects were at maximal effort. Further support for the likelihood that true maxima were obtained in both groups was that the maximal heart rates appeared maximal by sea level standards[1] and were similarly high in both the Tibetan and Han groups. Even if only Tibetans who achieved a plateau in oxygen consumption were compared, the Tibetans had higher maximal oxygen uptake than the Hans. We therefore conclude that the Tibetans had an increased maximal exercise capacity compared to the Han subjects.

Components of Oxygen Transport

We interpreted the increased maximal oxygen uptake to suggest that the Tibetans had an increased capacity to supply oxygen to working muscle in comparison to the Han young men. In order to assess which components of the oxygen transport chain were responsible, we compared the data obtained in the two groups pertaining to ventilation, alveolar-arterial oxygen diffusion, circulation and tissue oxygen diffusion to provide an indication of which component(s) might have been involved.

To identify whether oxygen transport from the atmosphere to the alveolus was enhanced in the Tibetans, we compared minute ventilation measured at rest and during submaximal and maximal exercise. The Tibetans had similar levels of ventilation for a given level of oxygen uptake at rest and during exercise (data not shown). This suggested that the Tibetans, unlike other high altitude lifelong natives,[20,24] may not hypoventilate but may maintain an equal ventilation at a given level of metabolic rate compared to acclimatized newcomers. However, at maximal exercise, the Tibetans had a greater maximal exercise ventilation than the Hans (see Table 12–1). The Tibetans achieved a greater maximal ventilation due to a larger tidal volume, not respiratory frequency (data not shown). Because the Tibetans had an increased resting vital capacity and chest circumference compared to the Hans,[21] it was likely that the Tibetans had a greater total lung volume. A larger lung volume could have permitted a greater tidal volume and consequently increased total ventilation without raising respiratory frequency. (This may have been important since increased respiratory frequency can potentially limit exercise by increasing symptoms of dyspnea.[2]) In addition, if lung volume were increased, the surface area for gas exchange and therefore the lung diffusing capacity would be expected to be enhanced. Larger lung volumes in association with increased lung diffusing capacities have been reported previously among lifelong residents of high altitude,[5,6,12,14] and pulmonary oxygen diffusing capacity has been suggested to limit exercise performance at high altitude.[26] Although alveolar to arterial oxygen diffusion was not measured in the present study, comparing the arterial oxygen saturation values obtained during progressive levels of submaximal to maximal exercise revealed a trend toward a higher arterial oxygen saturation for a given level of oxygen uptake in the Tibetans compared to the Hans,[21] suggesting that the Tibetans may have had a greater pulmonary oxygen diffusing capacity. In short, these considerations led us to conclude that the increased maximal ventilation, increased resting vital capacity and probable increase in total lung volume permitted an increased atmosphere to alveolus oxygen transport and contributed to the greater maximal oxygen uptake observed in the Tibetans.

Our information concerning circulation and tissue oxygen diffusion in the Tibetan compared to the Han young men was extremely limited. Given that the Tibetans and Hans had similar maximal heart rates but greater maximal oxygen consumption, the Tibetans had a greater oxygen pulse (oxygen consumption per heart beat) than the Hans (see Table 12–1). The greater oxygen pulse implied that the Tibetans had either increased oxygen utili-

zation (the product of arterial oxygen content and cardiac output) or tissue oxygen diffusion (the difference in arterial and venous oxygen content). Because the hemoglobin values at rest and the arterial oxygen saturation values at maximal effort were similar in the two groups (see Table 12–1), the arterial oxygen content at maximal effort was not likely to be greater in the Tibetans. However, stroke volume, cardiac output, and arterial and venous oxygen content were not measured and hence it could not be determined whether oxygen delivery or tissue oxygen utilization were greater in the Tibetan than the Han young men.

COMPARISON OF STUDY RESULTS WITH PREVIOUS COMPARISONS BETWEEN HIGH ALTITUDE NATIVES AND NEWCOMERS

The Tibetans achieved a higher maximal oxygen uptake by virtue of being able to exercise to a heavier maximal workload; the relationship between oxygen uptake and workload was the same in both groups (Fig. 12–1). However, the relationship between oxygen uptake and workload in the Tibetans and Hans differs from the relationship that we and others had previously observed in persons at sea level or after brief sojourn at high altitude[18] but agrees with previous observations by others[15] reporting that Peruvian high altitude natives had higher oxygen uptake for a given workload than acclimatized American or European newcomers. Duration of high altitude residence was unlikely to be responsible for raising oxygen uptake at a given workload since the Hans had oxygen uptake as high as the Tibetans or the Peruvians yet the Hans had lived at high altitude for shorter periods of time. One factor which the Tibetans, Hans and Peruvians shared was a smaller body size compared to the American or European subjects. Perhaps people of smaller stature are more prone to utilizing upper body muscles to supplement their leg muscles during bicycle exercise[15] or have a higher muscle to total body mass.

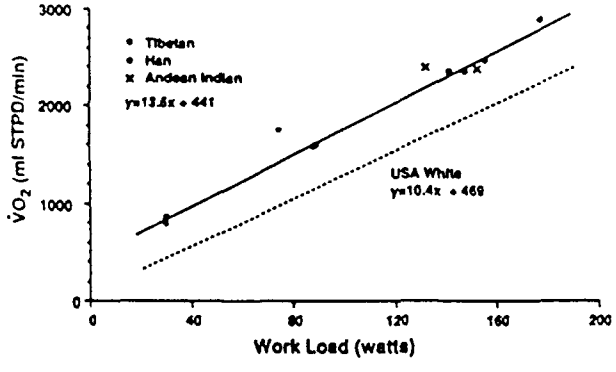

Figure 12–1 The mean values for oxygen uptake during progressive exercise up to and including maximal effort fall on the same regression line for Tibetan and Han subjects(—). Shown also are mean values previously reported for Peruvian natives at submaximal exercise.[15–17] The dashed line indicates the relationship obtained in 12 United States residents previously studied during cycle exercise at sea level and at 4,300 m.[18]

The higher maximal exercise capacity observed in the Tibetans compared to the Hans is supported by some, but not all, previous studies comparing native residents of high altitude.[10] One factor which appears related to previous comparisons is the extent of exercise training. Trained acclimatized newcomers have been shown in previous studies to have higher maximal oxygen uptakes than untrained acclimatized newcomers whereas untrained newcomers have generally performed less well than lifelong native high altitude residents.[10,11,15–17] Unknown for such comparisons has been the extent of exercise training in the high altitude residents. We therefore carefully selected subjects so as to obtain acclimatized newcomers and natives who were similar with respect to exercise training. Thus, the present report indicates that under circumstances in which both natives and newcomers are untrained, lifelong high altitude residents have modestly but significantly greater maximal oxygen uptake than acclimatized newcomers.

The duration of high altitude residence is another factor which may be important for interpreting the available literature on maximal exercise capacity. In reports in which the newcomers had resided for 6 months or less at high altitude, maximal heart rates were lower than those of lifelong natives or acclimatized newcomers residing at altitude for longer than 6 months.[10,16,19,22] Since maximal heart rate relates to oxygen uptake, studies of newcomers of relatively short duration at high altitude may underestimate the maximal oxygen uptake obtained. We therefore chose Han subjects who had lived at altitude for more than 6 months. Since the Hans and Tibetans demonstrated equally high heart rates at maximal effort, it appeared that the duration of high altitude residence among the Hans was sufficient to achieve truly maximal values. An even longer duration of high altitude exposure, encompassing the period of physical growth and development, appeared associated with a further increase in maximal oxygen uptake and this increase appeared independent of any additional rise in maximal heart rate.[10] Growth and development at high altitude is associated with attainment of larger lung volumes and lung diffusing capacity,[6,10,12,14] but whether developmental exposure contributes to the acquisition of larger hearts and tissue oxygen diffusing capacity is, to our knowledge, unknown.

To our knowledge, the present studies are the first measurements of maximal exercise capacity among Tibetan or Han residents of the Himalayan high altitude region. Table 12–2 compares these data with previous studies of Andean and European or American white high altitude natives and newcomers. Caution must be exercised in interpreting this data, given that a number of different investigators and study techniques were involved.

However, it is useful in two respects. First, comparing all the data from high altitude natives and acclimatized newcomers indicates that lifelong European or American white residents of high altitude have maximal oxygen uptakes that are, on the average, 7 ml/kg body weight greater than European or American white acclimatized newcomers. Similarly, Andean high altitude natives have maximal oxygen uptake that average 5 ml/kg body weight greater than Andean Indian acclimatized newcomers. Thus, the previously published data, when viewed in aggregate, support the conclusion of the present study, that maximal exercise capacity in the high altitude native is greater than in the acclimatized newcomer. Second, comparing the average value for each group of lifelong high altitude residents reveals that the European or American whites demonstrated lower maximal oxygen uptake than the Andean or the Himalayan subjects, suggesting that multiple generations of high altitude exposure may raise maximal exercise capacity above levels acquired as a result of lifelong high altitude exposure. Further, while the single value for the Tibetans is within the range of Andean values, it is interesting to note that it is at the upper end of that range and is equivalent to the maximal exercise capacity measured in a large sample of untrained young men residing at sea level[23]; this suggests some additional advantage may accrue from the even longer duration of high altitude residence likely to characterize Tibetans compared to Andean Indians. Needed, however, are more comparative studies using the same investigative techniques in carefully selected samples from populations whose duration of high altitude residence is well-established in order to determine whether differences in maximal oxygen transport capacity exist in Andean and Himalayan high altitude residents. Also required are comparisons with well-matched sea level groups or within the high altitude residents after prolonged sea level exposure to determine whether years to generations of high altitude exposure have restored maximal exercise capacity to sea level values.

SUMMARY AND CONCLUSIONS

Higher maximal oxygen uptake among Tibetan high altitude natives than acclimatized Han newcomers implies an increased capacity for oxygen supply or oxygen utilization by the working muscle. Our measurements supported the likelihood that increased exercise ventilation, vital capacity, and possibly pulmonary oxygen diffusing capacity permitted Tibetans to obtain greater maximal oxygen uptakes. Other factors including greater stroke volume and tissue oxygen diffusion may also have contributed to better exercise capacity in Tibetan and Han residents of 3,658 m. Unknown is whether the differences in maximal exercise capacity observed between the Tibetans and Hans stemmed from genetic factors or from developmental influences operating on the Tibetans who, unlike the Hans, had been born and raised at high altitude. Mechanisms by which lifelong hypoxic exposure and possibly genetic factors facilitate oxygen transport and utilization in the Tibetan population deserve further study.

TABLE 12-2 Exercise Performance of Young (20-30 yr) Male Lifelong High Altitude Residents (Natives) or People Who Have Moved From Low Altitude 2 Months or More Previously (Acclimatized Newcomers).

	Natives					*Newcomers*					
	Ref	*Alt*	*Wt*	*Max HR*	*Max $\dot{V}O_2$*	*Ref*	*Alt Yr*	*Alt*	*Wt*	*Max HR*	*Max $\dot{V}O_2$*
European or	11	3,100	68	193	46	10	1.4	3,400	71	187	38
American whites	6	3,100	69	182	40	15	0.2	4,000	79	183	38
	17	3,830	61	183	43	17	0.8	4,000	68	170	37
						19	0.4	5,800	64	144	33
Mean					43						36
Andean	10	3,400	59	196	46	10	1-4	3,400	59	193	38
Indian	17	3,830	60	188	47	10	14	3,400	61	193	46
	15	4,000	57	176	52						
	22	4,350	61	174	50						
	9	4,540	58		41						
Mean					47						42
Himalayan	—	3,658	56	191	56	--	8	3,658	54	187	46

Abbreviations: Ref = reference cited; Alt = altitude (m); Wt = body weight (kg); Max HR = heart rate at maximal effort (bpm); Max $\dot{V}O_2$ = oxygen consumption at maximal effort (ml_{STPD}/kg body weight); Alt Yr = years of altitude residence for newcomers.

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Internal Carotid Arterial Flow Velocity During Exercise In Tibetan and Han Residents of Lhasa (3658 m)

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Running Head: Exercise cerebral blood flow in Lhasa residents

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ABSTRACT

Cerebral blood flow increases with exercise at sea level but the increase is blunted after 18 to 21 days of high altitude exposure. Whether the response to exercise remains reduced after long-term exposure to high altitude is unknown. To determine whether high altitude residents increased their cerebral blood flow during exercise, we studied 15 male Tibetan lifelong residents and 11 male Han ("Chinese") 6.5±1.6 year residents of Lhasa (3658 m), Tibet Autonomous Region, China. The Tibetans and Hans were matched for age, body size, resting blood pressure, hemoglobin concentration, and diameter of the internal carotid artery. Noninvasive Doppler ultrasound was used to measure internal carotid arterial mean flow velocity and to assess cerebral blood flow and oxygen delivery. During submaximal exercise, both Tibetan and Han high altitude residents increased internal carotid arterial mean flow velocity and cerebral oxygen delivery. At maximal exercise, the Tibetans sustained the increase in flow velocity and cerebral oxygen delivery whereas the Hans did not. An increase in internal carotid arterial blood flow and a tendency toward higher arterial oxygen saturation contributed to greater cerebral oxygen delivery in the Tibetans compared to the Hans at maximal exercise. The greater cerebral oxygen delivery was associated with an increased maximal exercise performance. Therefore, our findings suggested that the cerebral blood flow response to exercise is restored after long-term residence at high altitude.

KEY WORDS: altitude, hypoxia, cerebral blood flow, oxygen delivery, Doppler ultrasound

APPENDIX II

Publications resulting to date from this research principally based on 1988 field studies:

Sun S, SY Huang, ZX Zhoma, JG Zhang, JX Tao, RG McCullough, RE McCullough, JT Reeves, LG Moore. Decreased ventilation and hypoxic ventilatory responsiveness are not reversed by nalaxone in Lhasa residents with chronic mountain sickness. FASEB J 3:A839, 1989.

Sun SF, CK Pickett, RG McCullough, SA Zamudio, A Micco, TS Droma, JG Zhang, Y Ping, A Cymerman and LG Moore. Chronic mountain sickness (CMS): Breathing and brain flood flow during sleep. FASEB J 4:A414, 1990.

Sun SF, SY Huang, JG Zhang, TS Droma, G Banden, RG McCullough, A Cymerman, JT Reeves and LG Moore. Decreased ventilation and hypoxic ventilatory responsiveness are not reversed by naloxone in Lhasa residents with chronic mountain sickness. Am Rev Resp Dis 142:1294-1300, 1990.

Moore LG, JG Zhuang, RG McCullough, A Cymerman, TS Droma, SF Sun, Y Ping and RE McCullough. Increased lung volumes in Tibetan high altitude residents. Am J Physical Anthropology 12 (supplement):341, 1991.

Droma TS, RG McCullough, RE McCullough, JG Zhuang, A Cymerman, SF Sun, JR Sutton, LG Moore. Increased vital and total lung capacities in Tibetan compared to Han residents of Lhasa (3658 m). In Press, Am J Physical Anthropology, 1991.

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p. A839

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DECREASED VENTILATION AND HYPOXIC VENTILATORY RESPONSIVENESS ARE NOT REVERSED BY NALOXONE IN LHASA RESIDENTS WITH CHRONIC MOUNTAIN SICKNESS. SF Sun, SY Huang, ZX Zhoma, JG Zhang, JX Tao, RG McCullough, RE McCullough, JT Reeves, and LG Moore. Tibet Inst of Medical Science, Shanghai Inst of Physiology and Univ of Colorado, Denver, CO

Persons with chronic mountain sickness (CMS) hypoventilate and are more hypoxemic than normals but the cause of the hypoventilation is unclear. Studies in 8 CMS patients and 4 healthy age-matched Lhasa, Tibet (3658m) residents were conducted to test the hypothesis that endogenous opioids depress ventilation and hypoxic ventilatory response (HVR) in CMS. Patients compared to controls had marked hypoventilation (higher end-tidal PCO_2), lower tidal volume (VT), blunted HVR A values, and a fall in $P_{ET}CO_2$ with O_2 breathing.

(*p<.01)	PETCO2	VT	HVR A	ΔPETCO2	FEV1	SaO2	Hgb
CMS pts	37.3*	0.55*	6*	-3.4*	2.81*	76*	24*
Controls	30.9	0.66	132	0.1	3.63	87	17

Naloxone infusion (0.14 mg/kg) to 6 CMS patients did not change resting VT, $P_{ET}CO_2$, HVR A value or arterial O_2 saturation (S_aO_2). Reduced forced expiratory volumes (FEV_1) suggested that CMS patients had mild airway obstructive lung disease which, together with hypoventilation, correlated closely with decreased S_aO_2 and elevated hemoglobin (Hgb) levels. Thus, while endogenous opioids were not implicated, the data *supported the* likelihood that central hypoxic ventilatory depression and blunted HVR reduced alveolar ventilation which, together with chronic lung disease, contributed to the hypoxemia and elevated Hgb levels.

FASEB J 3: A987, 1989

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CHRONIC MOUNTAIN SICKNESS (CMS): BREATHING AND BRAIN BLOOD FLOW DURING SLEEP. SF Sun, CK Pickett, RG McCullough, SA Zamudio, A Micco, TS Droma, JG Zhang, YangPing, A Cymerman, LG Moore, UCHSC, Denver, CO & Tibet Inst Med Sci, Lhasa, China.

CMS patients evidence exaggerated hypoxemia and polycythemia compared to healthy high altitude residents but whether hypoxemia is worsened during the night and decreases O_2 delivery is unknown. We performed breathing and brain blood flow (Doppler ultrasound) studies in 8 CMS and 8 well-matched control (CONT) residents of Lhasa (elev 3658m) during sleep. The occurrence of sleep-disordered breathing (SDB=#apneas +hypopneas/hr) was similar but episodes were longer in duration in CMS than CONT subjects. CMS subjects had lower mean S_aO_2 (HP Oximeter, %), greater desaturation (ΔS_aO_2, 90th-10th percentile of the S_aO_2 frequency distribution) and thus achieved lower minimum values during the night. Average nocturnal C_aO_2 (mls %) was similar but minimum values were lower in CMS than CONT subjects. (*$p<.05$)

	SDB	Duration	S_aO_2	ΔS_aO_2	MinS_aO_2	MinC_aO_2
CMS	12±6	24±5	66±5*	22±4*	55±7*	15±2*
CONT	10±6	14±1	86±2	5±1*	83±2	19±1

Internal carotid artery mean flow velocity (ICA MFV), an index of brain blood flow, was similar in CMS and CONT during wakefulness (12±2 vs 11±2 cm/sec) and sleep. During episodes of sleep-disordered breathing, ICA MFV fell modestly in CMS subjects (-7±4 %Δ) whereas it increased slightly in CONT (+6±2 %Δ, $p<.05$). Greater nocturnal desaturation and the absence of a compensatory increase in ICA MFV likely decreased brain O_2 delivery in CMS patients during the night. Prolonged hypoventilation rather than an increased number of discrete apneas or hypopneas may be responsible for the greater nocturnal desaturation observed.

Decreased Ventilation and Hypoxic Ventilatory Responsiveness Are Not Reversed by Naloxone in Lhasa Residents with Chronic Mountain Sickness[1-3]

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SUMMARY Persons with chronic mountain sickness (CMS) hypoventilate and are more hypoxemic than normal individuals, but the cause of the hypoventilation is unclear. Studies of 14 patients with CMS and 11 healthy age-matched control subjects residing in Lhasa, Tibet, China (3,658 m) were conducted to test the hypothesis that hypoventilation, blunted hypoxic ventilatory responsiveness (HVR), and hypoxic ventilatory depression of CMS were due to increased endogenous opioid production. Patients with CMS compared with control subjects exhibited hypoventilation (end-tidal carbon dioxide pressure [$P_{ET}CO_2$] = 36.6 ± 1.0 versus 31.5 ± 0.5 mm Hg, $p < 0.05$), lower tidal volume (V_T = 0.54 ± 0.02 versus 0.61 ± 0.02 ml BTPS, $p < 0.05$), blunted HVR (shape parameter A = 17 ± 8 versus 114 ± 22 mm Hg/L BTPS/min, $p < 0.05$), and a depressant effect of ambient hypoxia on ventilation ($\Delta P_{ET}CO_2$ with acute hyperoxia = −3.5 ± 0.5 versus −1.0 ± 0.6 mm Hg, $p < 0.05$). Reduced forced expiratory volume in 1 s to vital capacity ratios (FEV_1/VC) and a higher proportion of cigarette smokers in the group of patients with CMS compared with control subjects suggested that at least some patients with CMS had mild airway obstructive lung disease. Naloxone infusion (0.14 mg/kg) to six patients with CMS did not change resting V_T, $P_{ET}CO_2$, HVR, or Sa_{O_2}. Thus, although endogenous opioids were not implicated, the data suggested that blunted peripheral HVR and central hypoxic ventilatory depression reduced alveolar ventilation, and that alveolar hypoventilation together with chronic obstructive lung disease in some patients with CMS were responsible for the exaggerated hypoxemia characteristic of this disorder.

AM REV RESPIR DIS 1990; 142:1294-1300

Introduction

Persons with chronic mountain sickness (CMS) (synonyms: Monge's disease, excessive polycythemia) hypoventilate, have reduced levels of Sa_{O_2}, and develop excessive polycythemia compared with normal, high altitude residents. Although the exact prevalence for this syndrome is unknown, it is relatively common in high altitude communities, especially among older men (1). The pathogenic mechanisms for this syndrome involve alveolar hypoventilation (2–7), but the cause of the hypoventilation is unclear. A blunted hypoxic ventilatory response (HVR) has been observed in patients with CMS and has been postulated as an etiologic factor (3, 4); however, others have concluded that the presence of a depressed HVR is not causative because long-term, high altitude residents without CMS also have blunted HVR (3, 8). Therefore, factors other than, or in addition to, decreased HVR appear to be involved in reducing ventilation in CMS.

A well-known consequence of opiate drug administration is the depression of ventilation and HVR (9, 10). In newborn infants, inhibition of endogenous opioids by naloxone administration reversed the secondary, depressant effects of hypoxia on ventilation in newborn rabbits (11). Less convincing are the effects of naloxone administration on ventilation and HVR in adults, although some evidence exists to support the possibility that endogenous opioids exert inhibitory influences on ventilation in patients with obstructive lung disease (12) and in experimental animals during prolonged, severe hypoxia (13, 14).

CMS is characterized by prolonged, severe hypoxia and, in at least some patients, chronic lung disease. We therefore hypothesized that increased endogenous opioid production contributed to the hypoventilation of CMS. Our approach was to compare patients with CMS with healthy control residents of Lhasa, Tibet Autonomous Region, China, who were matched for age and duration of high altitude residence. CMS has been reported among Han (Chinese) who have moved from lowland China to Tibet and, albeit rarely, among Tibetans (1, 6). We measured the ventilatory responses to acute, progressive hypoxia and brief hyperoxia in the patients with CMS and the control subjects to evaluate the influences of an absence of a ventilatory increase with acute hypoxia and the presence of hypoxic ventilatory depression on alveolar ventilation. Because previous studies have shown that some patients with CMS have obstructive lung disease (8), we performed lung function measurements to assess the presence of lung disease and evaluated the contributions of impaired lung function and alveolar hypoventilation to the level of Sa_{O_2} observed. Patients with CMS were studied before and after the administration of naloxone, an endogenous opioid inhibitor, to evaluate the role of endogenous opioids in the determination of the ventilatory characteristics observed.

(*Received in original form December 7, 1989 and in revised form May 7, 1990*)

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[2] Supported in part by Grant No. 17-87-C7202 from the US Army Medical Research and Development Command, and by Grant Nos. NIH-HLBI 14895 and NIH-CHD 00681 from the National Institutes of Health.

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TABLE 1

VENTILATORY CHARACTERISTICS OF INDIVIDUAL CMS AND CONTROL SUBJECTS

Identification Number	Smoking (pack-years)	HGB (g %)	$P_{ET}CO_2$ (mm Hg)	ΔPCO_2 (mm Hg)	Sa_{O_2} (%)	HVR A	VT (L BTPS)	VC (L BTPS)	FEV_1/VC (%)
CMS subjects									
15a	—	25.5	34.8	−3.1	64	32	0.56	—	—
42a	29	22.7	41.2	−6.8	69	2	0.52	3.80	73
43a	13	23.3	41.9	−3.1	81	15	0.49	4.12	62
65a	1	22.4	31.7	−4.5	79	1	0.55	4.35	67
72a	15	23.4	38.5	−3.6	83	1	0.51	4.31	70
75a	40	22.3	35.9	−2.0	86	−13	0.51	3.90	89
76a	30	23.4	33.0	1.0	75	18	0.53	3.43	70
79a	24	25.1	41.6	−4.7	70	−9	0.49	3.41	75
8b	6	22.1	34.3	−2.7	81	111	0.58	4.66	86
16b	38	24.1	34.3	−5.3	52	33	0.36	3.36	77
19b	32	23.9	32.9	−1.4	79	22	0.68	4.61	73
20b	15	21.0	40.2	−5.2	76	9	0.55	4.68	89
24b	30	22.9	34.5	−2.5	67	−7	0.64	3.01	74
43b	30	22.3	38.1	−5.0	63	21	0.63	3.43	72
X	23*	23.2*	36.6*	−3.5*	73*	17*	0.54*	3.93	75*
SEM	3	0.3	0.9	0.5	2	8	0.02	0.16	2
Control subjects									
74a	0	18.4	29.2	−0.4	89	247	0.60	4.48	85
96a	0	14.5	32.6	1.5	85	63	0.57	4.98	83
97a	0	18.6	29.9	−2.0	89	78	0.70	4.16	75
98a	—	17.2	31.7	1.2	87	139	0.59	4.18	83
33b	12	18.1	32.6	−1.8	90	119	0.53	4.03	87
36b	0	16.6	31.3	−3.6	84	225	0.72	4.68	85
42b	0	19.8	29.6	0.3	80	151	0.56	3.68	85
45b	29	18.9	32.6	−1.0	86	23	0.66	3.43	78
49b	15	16.2	30.9	—	87	111	0.67	4.35	76
51b	13	15.9	31.2	0.1	88	65	0.60	3.23	83
54b	13	18.3	35.4	−3.8	81	31	0.53	4.28	82
X	8	17.5	31.5	−1.0	86	114	0.61	4.13	82
SEM	3	0.5	0.5	0.6	1	22	0.02	0.16	1

Definition of abbreviations: ID = subject identification number; HGB = hemoglobin, g/100 ml; $P_{ET}CO_2$ = end-tidal PCO_2; $\Delta P_{ET}CO_2$ = change in end-tidal PCO_2 from 70% O_2 to room air, mm Hg; Sa_{O_2} = arterial O_2 saturation, %; HVR A = hypoxic ventilatory response shape parameter A; VT = tidal volume, L BTPS; VC = vital capacity, L BTPS; FEV_1/VC = forced expiratory volume in 1 s to vital capacity ratio.

* $p < 0.05$.

Methods

Subjects

Studies were performed in the fall of 1987 and 1988 at the Tibet Institute of Medical Sciences in Lhasa, Tibet (3,658 m, PB 490 mm Hg) in 14 male patients with CMS and 11 healthy male control subjects. Subjects gave informed consent to study procedures approved by the University of Colorado Health Sciences Center and the Tibet Institute of Medical Sciences. A physician from the Tibet Institute of Medical Sciences served as medical monitor and was present throughout the study. Twelve of the 14 patients with CMS were Han who had been born at or near sea-level and who had migrated to Lhasa after 18 yr of age. The remaining two were Tibetans (identification no. 65a and 8b, table 1), one of whom who had been born and raised at low altitude in Sichuan Province and the other of whom was born and raised at 3,800 m and had lived at 4,500 m for the preceding 23 yr. Ten of the 11 control subjects were Han and one (identification no. 54b) was Tibetan.

Diagnosis of CMS was based on a blood hemoglobin level greater than 20 g/100 ml whole blood, a medical history showing a hemoglobin decrease after descent to sea level, and an absence of clear evidence of underlying left-sided heart or lung disease based on physical examination, resting electrocardiogram, and chest fluoroscopy. Hemoglobin levels of normal Han adult men in Lhasa averaged 16.95 g/100 ml whole blood (15, 16). Symptoms of CMS had been present for an average of 11 ± 2 yr. No patient was being treated with a respiratory stimulant at the time of study. Phlebotomy is not a routine treatment for CMS in Tibet and no patient had undergone phlebotomy within the past 3 yr. Additional symptoms present in most subjects with CMS were a plethoric and cyanotic appearance, complaints of fatigue with mild effort, headache and dizziness, and evidence of right-sided heart disease.

Equipment

Lung function measurements were made in standing subjects using a recording spirometer (13-L spirometer; Warren Collins, Braintree, MA) to which a helium meter and blower (Warren Collins) could be attached. The remaining ventilatory measurements were performed in seated subjects while they breathed through a bidirectional respiratory valve (Koegel, San Antonio, TX) from which end-tidal gases were sampled by a fuel cell O_2 analyzer (Model 101; Applied Technical Products, Denver, CO) and an infrared CO_2 capnograph (Model LB-2; Sensor-medics, Anaheim, CA). The gas analyzers were calibrated with gases analyzed on site using the Scholander technique. Minute ventilation ($\dot{V}E$) at rest and during O_2 breathing was measured with a Parkinson-Cowan dry gas meter and with the spirometer trace during the hypoxic and hypercapnic response tests. Sa_{O_2} was monitored by ear oximetry (Model 47201A; Hewlett-Packard, Waltham, MA). The electrical signals from the gas analyzers, the ear oximeter, and the dry gas meter were recorded using a 4-channel recorder (Model R304; Prime Line, San Francisco, CA). Respiratory frequency was counted from the end-tidal gas record.

Hemoglobin was measured in resting, seated subjects in duplicate from blood samples obtained without squeezing by finger stick, using a photometer (Hemo-Cue, Aktiebolaget Leo, Helsingburg, Sweden) that had been previously calibrated on site with samples analyzed spectrophotometrically using the cyanmethemoglobin technique. Hematocrit was measured using the microhematocrit technique from simultaneously obtained samples. In 49 comparisons, the hemoglobin value (y) measured by photometer correlated closely with the simultaneously determined microhematocrit (x) ($y = 0.28x + 2.8$, $r = 0.96$, $p < 0.0001$). Whereas the upper measurement limit for the photometer was 25.6 g/100 ml whole blood, the hemoglobin observed for the subjects with CMS was not different from the value predicted from the measured hematocrit value (difference between observed and predicted values = 0.1 ± 1.5 g/100 ml whole blood [SD]), implying that hemoglobin values were appropriate for the hematocrits observed.

Study Techniques

Subjects came to the laboratory after fasting for 2 to 4 h. FVC was measured in triplicate and the highest value accepted. FEV_1 was calculated from the FVC accepted. In seven of the patients with CMS and seven of the control subjects, expiratory reserve volume (VER) and FRC using a closed circuit helium rebreathing technique were measured in triplicate and averaged for calculating the residual volume (VR) and TLC. Measurements of TLC using helium rebreathing agreed to within 3.1 ± 3.1% (SEM) of values obtained by planimetry from chest X-rays (17).

While breathing room air, resting ventilation, Sa_{O_2}, and end-tidal gases were monitored for at least 5 min or until values became stable. For measuring O_2 consumption and CO_2 production, expired gas was collected in a meteorologic balloon for 3 min. The mixed expired O_2 and CO_2 fractions were measured using the dry gas meter and were corrected for the loss by gas sampling. Additional measurements of end-tidal CO_2 tension ($P_{ET}CO_2$) were made after 5 to 7 min of breathing 70% O_2 in N_2 (PI_{O_2} = 340 mm Hg).

TABLE 2

GROUP CHARACTERISTICS

	CMS	Control Subjects	p Value
Number	14	11	
Age, yr	49 ± 2	52 ± 1	NS
Height, cm	169 ± 2	168 ± 2	NS
Weight, kg	68 ± 2	63 ± 3	NS
Years of residence ≥ 3,600 m	27 ± 3	30 ± 2	NS
Hematocrit, %	72 ± 2	49 ± 2	< 0.01
O_2 consumption, ml STPD	286 ± 9	259 ± 13	NS
CO_2 production, ml STPD	214 ± 10	206 ± 8	NS
Ventilation, L BTPS	10.6 ± 0.5	11.4 ± 0.4	NS
$P_{ET}O_2$, mm Hg	60 ± 2	64 ± 1	< 0.05
HCVR S	0.98 ± 0.13	0.88 ± 0.13	NS
HCVR B	20.4 ± 2.3	21.4 ± 1.7	NS
HVR, $\Delta\dot{V}E/\Delta Sa_{O_2}$	0.001 ± 0.066	−0.283 ± 0.038	< 0.01

Definition of abbreviations: CMS = chronic mountain sickness; NS = not significant; $P_{ET}O_2$ = end-tidal P_{O_2}; HCVR = hypercapnic ventilatory response; HVR = hypoxic ventilatory response; S = slope; B = x-intercept.

The isocapnic HVR was measured in duplicate or triplicate using a modified rebreathing technique (18). Progressive hypoxia was induced over a 10-min period by having the subject rebreathe in a closed circuit from a spirometer initially containing room air. Thus, as the subject consumed the O_2 in the spirometer, the end-tidal P_{O_2} ($P_{ET}O_2$) and Sa_{O_2} values were reduced. Isocapnia was maintained at the $P_{ET}CO_2$ measured during room air breathing by regulating the amount of expired gas shunted through a canister containing CO_2 absorber. Ventilation was averaged over 30-s intervals and coordinated with the 30-s average $P_{ET}O_2$, $P_{ET}CO_2$, and Sa_{O_2} values. In the control subjects, the final 30-s average $P_{ET}O_2$ was 44 ± 1 mm Hg and the final Sa_{O_2} was 70 ± 1%. In the patients with CMS, the final 30-s average $P_{ET}O_2$ was 40 ± 1 mm Hg and the final Sa_{O_2} was 48 ± 2%. Curves relating ventilation and $P_{ET}O_2$ are hyperbolic in shape and were analyzed by fitting data to the hyperbolic equation $\dot{V}E = \dot{V}o + A/(P_{ET}O_2 - 32)$ where $\dot{V}E$ is ventilation in liters BTPS/min, $P_{ET}O_2$ is the end-tidal O_2 tension in mm Hg, $\dot{V}o$ is the ventilation asymptote, A is a shape parameter, and 32 is the $P_{ET}O_2$ asymptote. Curves relating ventilation and Sa_{O_2} are linear and were described by the slope, $\Delta\dot{V}E/\Delta Sa_{O_2}$. The shape parameter A and the slope $\Delta\dot{V}E/\Delta Sa_{O_2}$ were averaged from the three values measured for each subject.

The hypercapnic ventilatory response was measured using a modified rebreathing technique (19). The spirometer was filled with approximately 7 L of a gas containing 80% O_2 in N_2 in order to maintain $P_{ET}O_2$ above 250 mm Hg. As the subject rebreathed, a progressive rise in $P_{ET}CO_2$ of at least 10 mm Hg occurred within 7 to 10 min. Curves relating ventilation to $P_{ET}CO_2$ are linear and were analyzed by fitting the data to the simple linear equation $\dot{V}E = S(P_{ET}CO_2 - B)$ where S is the slope and B is the *x*-intercept.

Naloxone (DuPont Pharmaceuticals, Manati, PR) was administered by intravenous infusion through a polyethylene 20-g cannula inserted into an arm vein. Six patients with CMS received 8 to 10 mg per subject for an average dose of 0.14 mg/kg. One control subject (ID no. 74a) was given 6 mg or 0.10 mg/kg. Blood pressure by cuff and electrocardiogram were monitored throughout. Resting ventilation, HVR, and hyperoxic ventilatory response were measured immediately before naloxone administration and repeated 5 min after the completion of the naloxone infusion using the same measurement techniques described above.

Statistics

Values are reported as the mean ± 1 SEM in the figures, tables, and text. Patients with CMS and control subjects were compared using two-sample (Student's) *t* tests. Relationships between variables were evaluated using simple or multiple linear regression techniques. Changes within individuals before and after naloxone treatment were examined by paired *t* tests. Differences were considered significant when $p < 0.05$.

Results

The patients with CMS compared with the control subjects were similar in age, height, weight, and length of high altitude residence (table 2). All the patients with CMS smoked cigarettes, whereas half the control subjects were smokers (table 1). TLC, FRC, V_R (figure 1), and FVC (table 1) were similar in the patients with CMS and the control subjects. The FEV_1 tended to be lower (2.96 ± 0.17 versus 3.41 ± 0.14 L BTPS, respectively, $p = 0.07$), and the FEV_1/VC ratio was reduced in the patients with CMS compared with the control subjects (table 1).

Hemoglobin and hematocrit were increased, and Sa_{O_2} was decreased in the patients with CMS compared with the control subjects (tables 1 and 2). Resting O_2 consumption, CO_2 production, and $\dot{V}E$ (table 2) were similar but the patients with CMS had a lower V_T and a higher $P_{ET}CO_2$ than did the control subjects (table 1), implying a decreased effective alveolar ventilation. $P_{ET}O_2$ values were lower in the patients with CMS than in the control subjects (table 2) but not sufficiently low to account for the reduction in Sa_{O_2} (table 1), suggesting either a widening of the alveolar-arterial O_2 gradient or rightward shift of the hemoglobin-O_2 dissociation curve in the patients with CMS compared with the control subjects.

The HVR was decreased in the patients with CMS compared with the control subjects whether expressed as the $\Delta\dot{V}E/\Delta Sa_{O_2}$ (table 2) or the shape parameter A (table 1). The patients with CMS exhibited greater hyperventilation with acute hyperoxia than did the control subjects as measured by the $\Delta P_{ET}CO_2$ (table 1), implying that ambient hypoxia depressed resting alveolar ventilation in the patients with CMS. The HVR and the $\Delta P_{ET}CO_2$ with hyperoxia correlated nega-

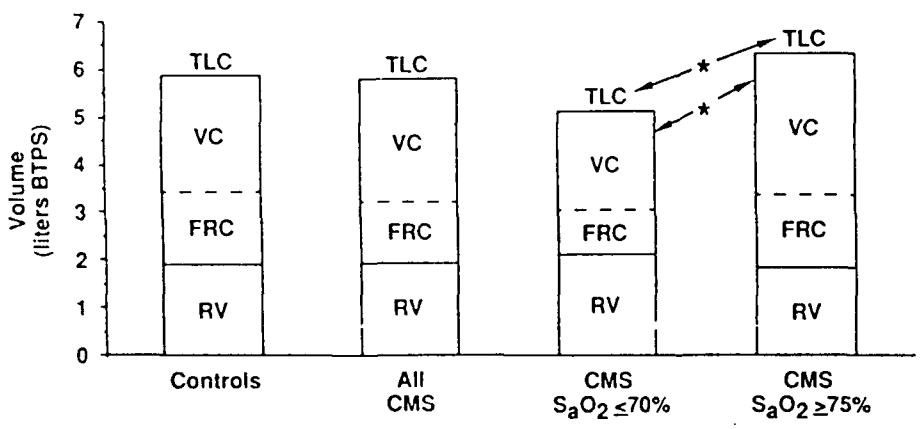

Fig. 1. Total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and residual volume (RV) are similar in the control and chronic mountain sickness (CMS) subjects. TLC and VC values were lower in the subset of patients with CMS whose arterial Sa_{O_2} values were less than 70% compared with those whose Sa_{O_2} values were greater than 75%.

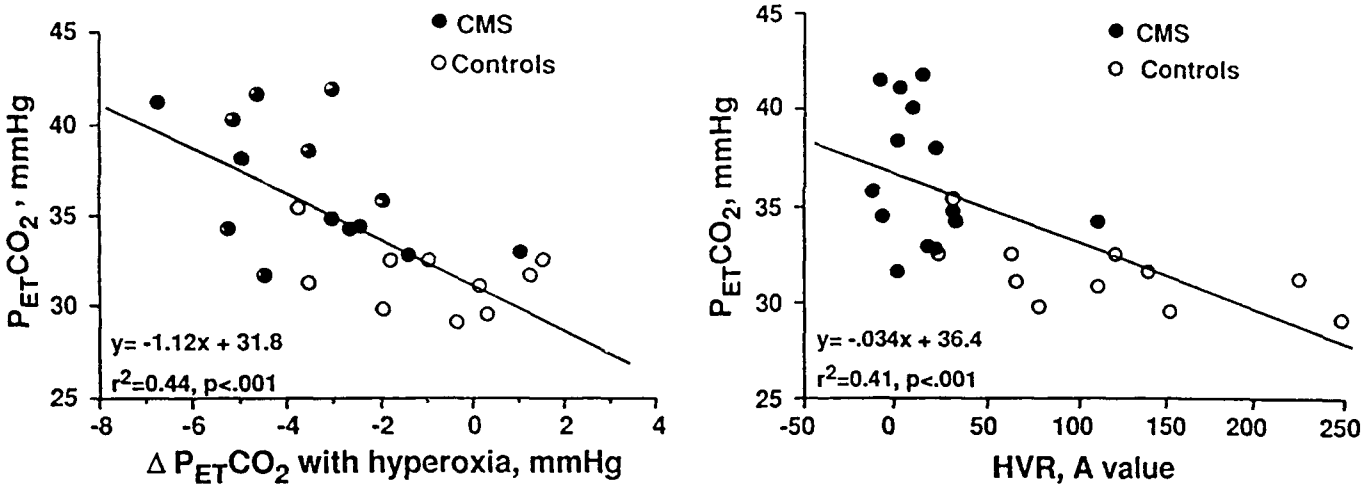

Fig. 2. *Left panel.* End-tidal P_{CO_2} (P_{ETCO_2}) while breathing room air was negatively correlated with the change in P_{ETCO_2} after 3 to 5 min of hyperoxia (ΔP_{ETCO_2}, P_{ETCO_2} while breathing room air minus P_{ETCO_2} while breathing 70% O_2 in N_2). The linear regression equation and proportion of the variance in P_{ETCO_2} that can be accounted for by the variance in ΔP_{ETCO_2} (r^2) are shown. *Right panel.* The P_{ETCO_2} while breathing room air was also correlated negatively with the hypoxic ventilatory response shape parameter A (HVR A value). The linear regression equation and r^2 value are shown.

tively with the P_{ETCO_2} among all subjects (figure 2). Use of a multiple regression equation revealed that 60% of the variation in P_{ETCO_2} could be accounted for by the HVR and ΔP_{ETCO_2} considered together ($y = -0.83\,\Delta P_{ETCO_2} - 0.02$ HVR A value + 33.8, $r^2 = 0.60$, $p < 0.0001$) that was greater than the variation in P_{ETCO_2}, which could be accounted for by either variable alone (figure 2). The ventilatory response to hypercapnia was similar in the patients with CMS and control subjects (table 2).

Lower Sa_{O_2} in the patients with CMS than in the control subjects could have been due to alveolar hypoventilation, a widening of the alveolar-arterial O_2 gradient, or a right-shifted hemoglobin-O_2 dissociation curve position. To consider the contribution of hypoventilation, we compared subgroups of patients with CMS and control subjects matched for lung function and smoking history (table 3). The patients with CMS had higher P_{ETCO_2} values and lower levels of Sa_{O_2} than did the control subjects (table 3). The differences between the subgroups were similar to those observed when all patients with CMS and control subjects were compared (table 1), suggesting that hypoventilation was the principal cause of the group differences in Sa_{O_2}. To consider the contribution of lung disease to the lower Sa_{O_2}, we compared the six subjects with CMS from the whole group whose $Sa_{O_2} < 70\%$ with the eight patients with CMS whose $Sa_{O_2} > 75\%$. The more hypoxemic subjects with CMS had lower VC and TLC (figure 1), lower FEV_1 values (2.52 ± 0.09 versus 3.24 ± 0.22 L BTPS, respectively, $p < 0.05$), and a trend toward longer smoking histories (30 ± 2 versus 19 ± 5 pack-years, $p = 0.06$). Because the P_{ETCO_2} was similar in the two groups of subjects with CMS (37 ± 1 versus 36 ± 1 mm Hg, p value was not significant), it appeared that impaired lung function was a major contributor to the variation in Sa_{O_2} among patients with CMS.

TABLE 3

CHARACTERISTICS OF CMS AND CONTROL SUBJECTS MATCHED FOR NORMAL PULMONARY FUNCTION (FEV_1/VC = 73 TO 89%) AND MODERATE SMOKING HISTORY (6 TO 29 PACK-YEARS)

	CMS	Control Subjects	p Value
Number	4	5	
Smoking history, pack-years	18 ± 5	16 ± 3	NS
FEV_1, L BTPS	3.38 ± 0.42	3.13 ± 0.19	NS
VC, L BTPS	4.14 ± 0.32	3.86 ± 0.23	NS
FEV_1/VC, %	81 ± 4	81 ± 2	NS
P_{ETCO_2}, mm Hg	39.3 ± 1.7	32.5 ± 4.8	< 0.05
Sa_{O_2}, %	74 ± 3	86 ± 2	< 0.05

For definition of abbreviations, see tables 1 and 2.

Naloxone administration to the patients with CMS did not change resting P_{ETCO_2}, Sa_{O_2}, the HVR A value (figure 3), the HVR $\Delta\dot{V}E/\Delta Sa_{O_2}$ (before = −0.01 ± 0.02 versus after = −0.05 ± 0.03, p value was not significant), ΔP_{ETCO_2} with hyperoxia (before = −4.2 ± 0.6 versus after = −5.8 ± 1.4 mm Hg, p value was not significant), or $\dot{V}E$ (before = 10.2 ± 0.7 versus after = 9.7 ± 0.6 L BTPS/min, p value was not significant). No change in any of the ventilatory parameters occurred in the one control subject after naloxone treatment (figure 3).

Discussion

We found that patients with CMS compared with healthy control residents of Lhasa, Tibet Autonomous Region (3,658 m), China, exhibited alveolar hypoventilation, blunted HVR, and hypoxic ventilatory depression that were not reversed by the administration of naloxone.

Hypoventilation in the patients with CMS compared with the control subjects was supported by the finding of higher P_{ETCO_2} values and lower V_T. The 5.1-mm Hg difference in P_{ETCO_2} levels observed between the patients with CMS and the control subjects compared favorably with the 5.6-mm Hg P_{CO_2} difference averaged for previous studies (20). The CMS and control groups were well matched with respect to age and duration of high altitude residence, implying that advancing age and/or prolonged high altitude exposure alone were not sufficient to produce CMS (21).

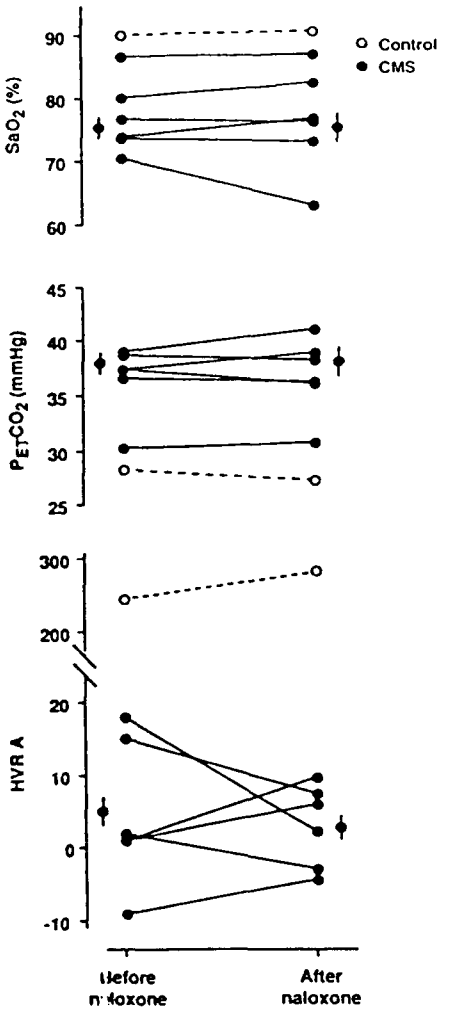

Fig. 3. Arterial Sa_{O_2}, end-tidal P_{CO_2} (P_{ETCO_2}), and the hypoxic ventilatory response A value (HVR A) were not changed by administration of naloxone in six patients with CMS or one control subject.

The cause of the hypoventilation observed in CMS has been attributed to a decreased ventilatory sensitivity to O_2 and CO_2. Concerning ventilatory sensitivity to CO_2, the patients with CMS and control subjects had equal hypercapnic ventilatory responses in this and in previous reports (3, 4, 8), and thus, decreased ventilatory sensitivity to CO_2 was not a likely contributor to the relative hypoventilation observed. Concerning the ventilatory sensitivity to O_2, most but not all previous studies have observed a decreased HVR in patients with CMS compared with control subjects (3–5, 8, 22). The reduction in HVR in the present study was evident whether values were expressed as the shape parameter A or the $\Delta \dot{V}E/\Delta Sa_{O_2}$, or whether values were compared with those obtained using the same techniques in younger Han male residents of Lhasa (23), middle-aged Han men living at 1,600 m (24), and whites of the United States residing at 1,600 or 3,100 m (8, 24). We were careful to give sufficient hypoxia to produce at least an equal fall in Sa_{O_2} in the CMS and the control groups, even though this meant that values reached absolutely lower levels in the subjects with CMS. Not only was HVR lower in the patients with CMS compared with the control subjects, but the decrease in hypoxic sensitivity related to the elevation in P_{ETCO_2} among all subjects (figure 2). We therefore concluded that decreased HVR contributed to the relative hypoventilation observed in the patients with CMS compared with the control subjects.

Blunted HVR is not likely to be the only factor involved in the development of CMS because persons with blunted or absent hypoxic ventilatory drives live successfully at high altitude for many years and some persons with the disorder have hypoxic responses within the normal range (8). It is recognized that in addition to the stimulatory effect of hypoxia on the carotid body, hypoxia also acts at central sites to depress ventilation. Whereas greater hypoxic ventilatory depression and low initial HVR characterize persons who develop acute mountain sickness (25), the involvement of hypoxic ventilatory depression in CMS has not been thoroughly investigated. To examine the depressant effect of hypoxia on ventilation, we measured the change in P_{ETCO_2} with acute (3 to 5 min) hyperoxia. Because hyperoxia produced a fall in P_{ETCO_2} in the patients with CMS but not the control subjects, we concluded that the ambient hypoxia of high altitude exerted a depressant effect on ventilation. Although, in general, acute hyperoxia induced a greater fall in P_{ETCO_2} in those persons with low HVR, there were individual exceptions. As a result, the two factors together were able to account for 60% of the variation in effective alveolar ventilation (resting P_{ETCO_2} while breathing room air), which was significantly greater than the 41 to 44% of the variation in P_{ETCO_2} that could be accounted for by either factor alone (figure 2). The presence of a stimulatory effect of hyperoxia on ventilation in patients with CMS has been reported previously (3, 8, 26), but studies were performed in only a small number of subjects with CMS without similar measurements being obtained in control subjects, and the contribution of the depressant effect of hypoxia to the hypoventilation of CMS was not considered. Thus, we concluded that the presence of a central, depressant effect of hypoxia together with the absence of peripheral ventilatory sensitivity to hypoxia decreased alveolar ventilation in the subjects with CMS.

We hypothesized that the hypoventilation, blunted HVR, and greater hypoxic ventilatory depression observed in the subjects with CMS were due to increased endogenous opioid production. Opioids are known to depress ventilation and HVR (9). These depressant effects are quickly relieved by administration of the opioid inhibitor naloxone. In favor of the hypothesis was evidence that naloxone reversed the secondary, depressant effects of hypoxia on ventilation in neonatal rabbits (11) and attenuated the ventilatory depressant effect of severe hypoxia in adult experimental animals (13, 14). Against the hypothesis were studies indicating that endogenous opioids were not increased during hypoxia (27), that naloxone did not increase ventilation even in settings where the levels of endogenous opioids were increased (28), and that naloxone did not decrease hypoxia-induced ventilatory depression in adults (29).

To determine whether endogenous opioids acted as a ventilatory depressant in CMS, we administered naloxone to six patients with CMS and to one control subject. We did not find any effect of naloxone on ventilation, HVR, or hypoxic ventilatory depression in any subject. The naloxone dose administered averaged 0.14 mg/kg and ranged from 0.12 to 0.16 mg/kg in individual subjects. This dose exceeded that required to fully antagonize morphine and achieve complete inhibition of the μ-receptor to which beta-endorphins bind and approximated the 0.15 mg/kg dose required to achieve complete inhibition of all three receptors to which enkephalins, benzomorphans, metenkephalins, morphine, and beta-endorphins bind (10). However, our dose was below the 0.2 to 4 mg naloxone/kg range used in previous studies in which ventilatory effects of naloxone were observed (11, 13, 14), suggesting that higher doses are required to achieve complete inhibition of endogenous opioids or that other, nonopioid antagonist effects of the drug were involved in the changes observed. In any event, because we observed no effect of naloxone at a dosage that was likely to have been sufficient to inhibit endogenous opioids, we concluded that endogenous opioids were not involved in the hypoventilation of CMS. Thus, the working hypothesis was not substantiated.

The factors responsible for the hypoxemia of CMS deserve consideration. The

patients with CMS could have been more hypoxemic than were the control subjects due to hypoventilation serving to decrease alveolar P_{O_2}; to impaired diffusion, ventilation:perfusion inhomogeneity, or shunting acting to widen the alveolar-arterial O_2 gradient; or to a rightward shift of the hemoglobin-O_2 dissociation curve. To assess the contribution of hypoventilation, we matched subgroups of CMS and control subjects with similar lung function and smoking history. Because the CMS subgroup had higher P_{ETCO_2} and lower Sa_{O_2} levels than did the control subjects and because the differences were of the same magnitude as those seen between all the CMS and control subjects, we concluded that hypoventilation was the major factor responsible for the lower Sa_{O_2} levels observed in the patients with CMS. To assess the contribution of lung disease, we compared subgroups of patients with CMS with the lowest and highest extremes of Sa_{O_2}. Because the subgroup with the lowest Sa_{O_2} had poorer lung function but similar alveolar ventilation when compared with the control subjects, we concluded that poorer lung function and presumably a widened alveolar-arterial O_2 gradient were responsible for the exaggerated hypoxemia observed in some patients with CMS.

Thus, the present study supports previous studies that have emphasized the importance of hypoventilation in accounting for the exaggerated hypoxemia of CMS (3–5, 22, 30, 32) and also indicates that additional factors involving a widening of the alveolar-arterial O_2 gradient are likely to be involved in at least some patients. A widened alveolar-arterial O_2 gradient has been reported previously in patients with CMS compared with control subjects (8), averaging 7 mm Hg in the normal subjects and 10 to 11 mm Hg in the patients with CMS studied in Lhasa during room air breathing (1). The markedly lower levels of Sa_{O_2} relative to the P_{ETO_2} present in the patients with CMS compared with the control subjects at the end of the HVR test supports a widening of the alveolar-arterial O_2 gradient in the present study. A widened alveolar-arterial O_2 gradient may, in turn, be due to impaired diffusion secondary to lung disease and/or ventilation:perfusion inhomogeneity. Early reports noted the frequency of lung disease in persons with the disorder (2), and half the patients studied at 3,100 m in Leadville, Colorado had some degree of chronic lung disease (8). Even though none of the subjects with CMS presented clear evidence of lung disease, the measured FEV_1 probably understated the magnitude of the lung disease because the reduced density of the air at high altitude allows for more rapid exhalation (31). Concerning ventilation:perfusion inhomogeneity, Cruz and colleagues (33) have shown that phlebotomy raised arterial O_2 tensions in patients with CMS as a result of likely improvement in ventilation:perfusion matching. Lastly, comparing the Sa_{O_2} values obtained with arterial P_{O_2} values reported previously in five patients with CMS and 10 control subjects in Lhasa (1) suggests that the hemoglobin-O_2 dissociation curve position was not different in the two groups.

In summary, the hypoventilation characteristic of CMS appeared to be due principally to the combined effects of decreased HVR and the presence of hypoxic ventilatory depression. Endogenous opioids were not implicated in diminishing HVR or eliciting hypoxic ventilatory depression, but the responsible factors were not identified in this study. We may speculate that one or more of a series of factors, including low initial HVR, prolonged residence at high altitude, chronic lung disease, heightened pulmonary vascular reactivity, or susceptibility to sleep apnea syndromes, could be involved in exaggerating hypoxemia and that the exaggerated hypoxemia, by depressing ventilation, further perpetuates the condition. The preponderance of Hans versus Tibetans among the patients with CMS in our sample and in a previous report (1) raises the possibility that the genetic background of the individual is also important for deciding susceptibility. CMS is a clear instance of adaptive failure at high altitude and probably contributes to the increased mortality from lung disease at high altitude (34) and to the increased emigration of elderly reported in North America from a high altitude to a low altitude (35). Prospective studies are required to determine the sequence of events involved in its development.

Acknowledgment

The cooperation of the volunteer subjects and the extensive assistance received from Drs. Tse Ren Zhou Ga and Tuedeng of the Tibet Autonomous Region Ministry of Health and Drs. Shang-Wen Fang, De-Cai Zhang, and W-H Zhang of the People's Provincial Hospital made this study possible. Dr. John Holaday from Walter Reed Army Institute of Research kindly provided advice concerning the naloxone studies and Dr. Garrison Rapmund provided advice and encouragement throughout.

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American Journal of Physical Anthropology
vol 12 (supplement): 341, 1991

Increased Lung Volumes in Tibetan High Altitude Residents. L.G. MOORE, J.G. ZHUANG, R.G. MCULLOUGH, A. CYMERMAN, T.S. DROMA, S.F. SUN, Y. PING, R.E. MCCULLOUGH. Tibet Inst Med Sci & Univ Colorado at Denver & Health Sci Ctr, Denver, CO.

Larger chest dimensions have long been noted in Andean high altitude residents. The limited information previously available from the Himalayas has prompted speculation as to whether "barrel-shaped" chests and larger lung volumes are confined to Andean residents.

Our approach was to compare residents of Lhasa, Tibet, China (elev 3658m) who were either lifelong high altitude residents (Tibetans, n=23) or acclimatized newcomers (Han "Chinese", n=23). The Hans had been born at or near sea level, migrated to high altitude as children (n=4) or adults (n=19), and lived in Lhasa 5±1 yrs. The Tibetans and Hans were similar in age, height, weight, body surface area, hemoglobin level and smoking history (2±0, 1±0 pk yrs). Forced vital capacity (FVC) was greater in Tibetans than Hans (table) but similar in Han child vs adult migrants (data not shown). FVC was related to chest dimension among all subjects ($y=113.2x-4782$, $R^2=.48$, $p<.05$) measured at end normal expiration. Using the helium dilution technique, the Tibetans had greater functional residual capacity (FRC), residual volumes (RV) and total lung capacities (TLC). (*=p<.05; all values BTPS)

	FVC,l	FRC,l	RV,l	TLC,l
Tib	4.93±.11*	3.70±.15*	1.86±.12*	6.80±.19*
Han	4.67±.12	3.40±.10	1.56±.09	6.24±.18

The Tibetans' larger TLC (9%) was due chiefly to increased RV (19%) with proportionately less increase in FVC (5%).

These are, to our knowledge, the first measurements of lung volumes in Himalayan residents. Compared to Andean values, the Tibetans were taller, leaner and had equal or larger vital capacities relative to body size (3.05 l/m^2 BSA, 40.3 mls/cm ht) than Andean natives (2.72 l/m^2, 31.5 mls/cm) (Hurtado '32, Brody '77). Thus, Tibetans appear to have larger lung volumes than acclimatized newcomers (Hans) and values at least as great as Andean high altitude residents. The increase in residual volume may facilitate gas exchange and maintenance of arterial O_2 saturation during exercise, thereby contributing to the greater maximal O_2 uptake reported in Tibetan compared to Han Lhasa residents (Resp. Physiol. 79:151,1990).

Supported in part by grants NIH-HL14985 and HD000681, NSF-BNS8919645 and U.S.Army DAMD-17-87C7202).

INCREASED VITAL AND TOTAL LUNG CAPACITIES IN TIBETAN COMPARED TO HAN RESIDENTS OF LHASA (3658 M)

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Running head: Tibetan Lung Volumes

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ABSTRACT

Larger chest dimensions and lung volumes have been reported for Andean high-altitude natives compared with sea-level residents and implicated in raising lung diffusing capacity. Studies conducted in Nepal suggested that lifelong Himalayan residents did not have enlarged chest dimensions. To determine if high-altitude Himalayans (Tibetans) had larger lung volumes than acclimatized newcomers (Han "Chinese"), we studied 38 Tibetan and 43 Han residents of Lhasa, Tibet Autonomous Region, China (elev 3658 m) matched for age, height, weight and smoking history. The Tibetan compared with the Han subjects had a larger total lung capacity (6.80±0.19 *vs* 6.24±0.18 l BTPS, $p<0.05$), vital capacity (5.00±0.08 [mean±SEM] *vs* 4.51±0.10 l BTPS, $p<0.05$), and tended to have a greater residual volume (1.86±0.12 *vs* 1.56±0.09 l BTPS, $p=0.06$). Chest circumference was greater in the Tibetan than the Han subjects (85±1 *vs* 82±1 cm, $p<0.05$) and correlated with vital capacity in each group as well as in the two groups combined ($r=0.69$, $p<0.05$). Han who had migrated to high altitude as children (≤ 5 yrs old, n = 6) compared to Han adult migrants (≥ 18 yrs old, n = 26) were shorter but had similar lung volumes and capacities when normalized for body size. The Tibetans' vital capacity and total lung capacity in relation to body size were similar to values reported previously for lifelong residents of high altitude in South and North America. Thus, Tibetans, like North and South American high-altitude residents, have larger lung volumes. This may be important for raising lung diffusing capacity and preserving arterial oxygen saturation during exercise.

Key Words: vital capacity, residual volume, chest dimensions, hypoxia, growth and development

APPENDIX III

Publications resulting to date from this research principally based on 1990 field studies:

McCullough RG, RE McCullough, JG Zhuang, TS Droma, SF Sun, A Cymerman, Jr Sutton, G Rapmund, LG Moore. Increased total lung capacities in Tibetan compared to Han residents of high altitude. Hypoxia '91 (In Press).

Groves BM, JR Sutton, TS Droma, RG McCullough, G Rapmund, SF Sun, JG Zhuang, RE McCullough and LG Moore. Absence of hypoxic pulmonary hypertension in normal Tibetans at 3,658 M. Seventh International Hypoxia Symposium. Lake Louise, Alberta, February, 1991.

Zhuang JG, TS Droma, JR Sutton, B Groves, G Rapmund, C James, SF Sun, and LG Moore. Sympathetic and parasympathetic influences during exercise in Tibetan and Han ("Chinese") residents of Lhasa (3658M). Seventh International Hypoxia Symposium. Lake Louise, Alberta, February, 1991.

Sutton JR, BM Groves, RE McCullough, RG McCullough, TS Droma, JG Zhuang, G Rapmund, SF Sun, and LG Moore. Oxygen transport in Tibetan residents of Lhasa 3658 M. Seventh International Hypoxia Symposium. Lake Louise, Alberta, February, 1991.

SEVENTH INTERNATIONAL HYPOXIA SYMPOSIUM
McMASTER UNIVERSITY, THE ARCTIC INSTITUTE OF NORTH AMERICA

FEBRUARY 26 - MARCH 2, 1991

INCREASED TOTAL LUNG CAPACITIES IN TIBETAN COMPARED TO HAN HIGH ALTITUDE RESIDENTS.

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Larger chest dimensions and lung volumes have been seen in Andean high altitude natives and implicated in raising lung diffusing capacity. Limited information from Nepal suggests that Himalayan natives do not have enlarged chest dimensions. To determine if high altitude Himalayans (Tibetans) had larger lung volumes than acclimatized newcomers (Han "Chinese"), we studied 39 Tibetan and 43 Han residents of Lhasa, Tibet (3658m) matched for age, height, weight and smoking history. The Tibetans had larger vital and total lung capacities than the Hans and tended to have greater residual volume.

	VC, l BTPS	RV, l	TLC, l
Tibetan	$5.00 \pm .08^{*}$	$1.86 \pm .12^{+}$	$6.80 \pm .19^{*}$
Han	$4.51 \pm .10$	$1.56 \pm .09$	$6.24 \pm .18$

($^{*}p<0.05$, $^{+}0.05<p<0.10$)

Chest circumference was greater in Tibetans than Hans (85 ± 1 *vs* 82 ± 1cm, $p<0.05$). Thus Tibetans, like Andeans have increased lung volumes at high altitude. This may be important for raising lung diffusing capacity and preserving arterial O_2 saturation during exercise.

Supported in part by grants from the NIH, the NSF, and the U.S. Army.

SEVENTH INTERNATIONAL HYPOXIA SYMPOSIUM
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FEBRUARY 26 - MARCH 2, 1991

ABSENCE OF HYPOXIC PULMONARY HYPERTENSION IN NORMAL TIBETANS AT 3,658M

GROVES B.M., J.R. SUTTON, T.S. DROMA, R.G. MCCULLOUGH, G. RAPMUND, S.F. SUN, J.G. ZHUANG, R.E. MCCULLOUGH, L.G. MOORE. Tibet Inst Med Sci, Lhasa, Tibet & U Colo Hlth Sci Ctr, Denver, CO 80262.

Elevated pulmonary arterial mean pressures (PAM, mmHg) in high altitude residents may be maladaptive. If so, well-adapted populations should have low pressures. We catheterized 5 normal Tibetan men (22 yrs, 1.62 m^2 BSA) in Lhasa.

	REST (sitting)		EXERCISE (ergometer)			
Watts	0	0	60	121	179	158
P_aO_2	54	36	56	53	55	345
~~PAM~~ 14.5	15	19	25	32	32	33
C.O.	5.1	5.6	10.6	15.7	19.4	16.9
PVR	1.7	2.6	1.6	1.5	1.0	1.1

At rest, the subjects had normal mean PAM and PVR (Wood u) and did not develop pulmonary hypertension while breathing 14% O_2. Near maximal exercise (179 watts, 93% VO_2max) slightly increased PAM but not PVR. Breathing 100% O_2 did not reduce PAM or PVR during exercise. Compared to literature values, the Tibetans' PAM was markedly lower than North or South Americans' at similar altitudes. The Tibetans' minimal hypoxic pulmonary vasoconstriction and marked increase in exercise cardiac output (C.O., l/min) is indicative of remarkable high altitude adaptation.

Supported by grants from the NIH, NSF, and U.S. Army.

SEVENTH INTERNATIONAL HYPOXIA SYMPOSIUM
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FEBRUARY 26 - MARCH 2, 1991

SYMPATHETIC AND PARASYMPATHETIC INFLUENCES DURING EXERCISE IN TIBETAN AND HAN ("CHINESE") RESIDENTS OF LHASA (3658M).

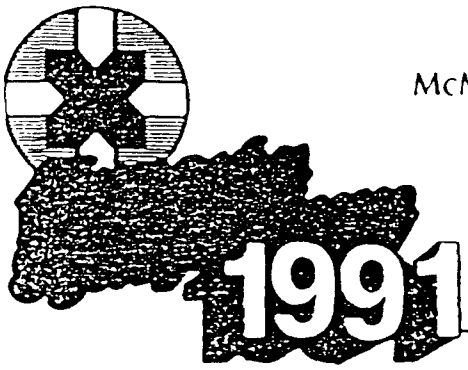
ZHUANG J.G., T.S. DROMA, J.R. SUTTON, B. GROVES, G. RAPMUND, C. JANES, S.F. SUN, L.G. MOORE. Tibet Inst Med Sci, Lhasa, Tibet & U Colo Hlth Sci Ctr, Denver, CO.

To test the hypothesis that native high altitude residents have more parasympathetic and less sympathetic tone than newcomers, we compared the effects of sympathetic (0.2 mg/kg i.v. propranolol) and parasympathetic blockade (0.04 mg/kg i.v. atropine) in 10 Tibetans and 9 Hans who had lived >3600m for 2 yrs. Each subject was studied during progressive cycle exercise (1) to establish VO_2max, (2) with an arterial line in place (CON), (3) after propranolol (PRO), and (4) after atropine (ATR) treatment.

In study #1, the Tibetans achieved a higher VO_2max than the Hans (43.8 *vs* 38.7 mls/kg) at equal HRs (180 *vs* 181 bpm).

	CON:HR	VO_2max	PRO:ΔHR	ΔVO_2	ATR:ΔHR	ΔVO_2
TIB	181	42.1	-41	-3.7	+5	-3.0
HAN	188	39.6	-55	-5.0	-6	-3.5

Compared to values achieved during CON, PRO had less effect on HR in the Tibetans than the Hans (Table). ATR increased HR in the Tibetans and decreased HR in the Hans. Neither PRO or ATR changed VO_2max. Thus, the results supported the study hypothesis and suggested that Tibetans achieved greater VO_2max than the Hans with less sympathetic and greater parasympathetic activity.



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FEBRUARY 26 - MARCH 2, 1991

OXYGEN TRANSPORT IN TIBETAN RESIDENTS OF LHASA 3658M

J.R. SUTTON, B.M. GROVES, R.E. McCULLOUGH, R.G. McCULLOUGH, T.S. DROMA, J.G. ZHUANG, G. RAPMUND, S.F. SUN & L. MOORE.

Cumberland College of Health Sciences, Sydney, Australia, Tibet Institute of Medical Sciences, Lhasa, University of Colorado Health Sciences Centre, Denver, Co.

The purpose of this study was to examine individual components of the oxygen cascade during exercise in young healthy Tibetan residents of Lhasa 3658M. 5 males aged 22 yrs, VO_2max, 45 $mlsO_2/kg/min$ were studied at rest and during exercise with indwelling pulmonary and radial or brachial artery catheters. Results

Work (WATTS)	60	121	179
% VO_2max	44	73	91
$P(I-A)O_2$mmHg	29.8	26.5	24.1
$P(A-a)O_2$mmHg	6.9	13.2	14.3
$C(a-v)O_2$ mls/L	105	124	134
PvO_2	23.5	20.4	19.0

The major adaptations in oxygen transport during exercise are seen in $P(I-A)O_2$ gradient and PvO_2. For a given VO_2 the $P(A-a)O_2$ and $C(a-\bar{v})O_2$ are similar to those seen at sea level and high altitude in sea level dwellers. Thus the major adaptations observed in Tibetans at Lhasa are determined by increases in ventilation (PCO_2 26.3 mmHg) and by increases in oxygen extraction.

APPENDIX IV

Related publications from research sponsored by other agencies

National Science Foundation

Zhoma ZX, SF Sun, JG Zhang, SY Hu[illegible], LG Moore. Fetal growth and maternal 02 supply in Tibetan and Han residents of Lhasa (3658 M). FASEB J 3:A987, 1989.

Zamudio SA, TS Droma, TE Dahms, SK Palmer and LG Moore. Uterine blood flow, vascular resistance and blood volume during high altitude pregnancy. FASEB J 4:A414, 1990.

Moore LG. Maternal 02 transport and fetal growth in Colorado, Peruvian, and Tibetan populations. Am J Physical Anthropology. 78:274, 1989.

Moore LG. Maternal 02 transport and fetal growth in Colorado, Peruvian, and Tibetan populations. Am J Hum Biol 2:627-638, 1990.

Zamudio SA, TS Droma, SK Palmer, J Berman, TE Dahms, RE McCullough, RG McCullough and LG Moore. Blood volume expansion and pregnancy outcome in high altitude pregnancy. Am J Phys Anthropology 12 (Suppl):187, 1991.

Zamudio SA, SK Palmer, J Berman, RE McCullough, RG McCullough and LG Moore. Circulatory changes in normal versus hypertensive pregnancy at high altitude. Seventh International Hypoxia Symposium, Lake Louise, Alberta, February, 1991.

National Heart, Lung and Blood Institute

Wolfel EE, BM Groves, GA Brooks, GE Butterfield, RS Mazzeo, LG Moore, JR Sutton, PR Bender, TE Dahms, RE McCullough, RG McCullough, SY Huang, SF Sun, RF Grover, HN Hultgren and JT Reeves. Oxygen transport during steady-state sub-maximal exercise in chronic hypoxia. J Appl Physiol 70(3): 1129-1136, 1991.

FASEB JOURNAL, VOL 3, 1989

p. A907

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FETAL GROWTH AND MATERNAL O_2 SUPPLY IN TIBETAN AND HAN RESIDENTS OF LHASA (3658M). ZX Zhoma, SF Sun, JG Zhang, SY Huang, Zhang and LG Moore. Tibet Inst of Medical Science, Shanghai Inst of Physiology and Univ of Colo, Denver, CO

Fetal growth retardation at high altitude suggests that maternal O_2 supply is insufficient to meet fetal demands. We hypothesized that decreased uterine blood flow reduced uterine O_2 delivery to retard fetal growth and that long resident high altitude populations better maintained uterine blood flow and hence fetal growth. Studies were conducted in Tibetans (n=9 nonpregnant, n=18 pregnant) lifelong high altitude residents descended from many generations of high altitude ancestors and Han (Chinese) (n=9 nonpregnant, 10 pregnant) sea level natives who had migrated to altitude as adults. Full-term Tibetan babies weighed more than their Han counterparts (3307±110 vs 2657±78 g, p<.01). Tibetans evidenced a greater fall in end-tidal PCO_2 (-4±1 vs -2±1 mmHg, p<.05) with pregnancy than Hans, implying greater effective alveolar ventilation. Hemoglobin fell with pregnancy, especially among Tibetans, such that the Tibetans had lower hemoglobin (13±0 vs 14±0 gms%, p<.05) and arterial O_2 content (16±0 vs 17±1 mls O_2/100 ml) values. Doppler mean flow velocimetry of the common iliac and uterine arteries was used to provide an indication of uterine blood flow. The Tibetans had a higher ratio of uterine artery MFV to common iliac MFV than the Hans and the ratio was correlated positively with birth weight (r=.69, p<.05). Uterine artery mean flow velocity (MFV) tended to be greater in Tibetans than Han (48±2 vs 43±2 cm/sec, p=.10). We therefore concluded that the Tibetans' resistance to high altitude fetal growth retardation was not afforded by increased arterial O_2 content but may involve blood flow redistribution to favor the uterine circulation.

FASEB J 3: A987, 1989

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UTERINE BLOOD FLOW, VASCULAR RESISTANCE AND BLOOD VOLUME DURING HIGH ALTITUDE PREGNANCY. S.A. Zamudio, T.S. Droma, T.E. Dahms, S.K. Palmer and L.G. Moore. Univ.of Colorado Health Sciences Center and Denver Campuses, Denver, CO 80262.

Birth weight decreases with increasing altitude and under other conditions in which maternal O_2 transport is limited, suggesting that decreased uterine O_2 delivery retards fetal growth. To date we have studied 31 pregnant residents of Leadville, CO (elev 3100m) at weeks 12 (n=11), 24 (n=11) or 36 (n=13) to investigate factors influencing uterine blood flow during high altitude pregnancy. Uterine artery mean flow velocity (UA MFV, measured by Doppler ultrasound) increased nearly twofold from 12 to 36 weeks of pregnancy. The early (12→24 wk) increase was accompanied by expansion of total blood volume (measured by carbon monoxide rebreathing) and by decrements in the UA mean peak systolic/mean end diastolic (A/B) ratio. The later (24→36 wk) increase was paralleled chiefly by an increased UA/common iliac MFV (UA/CI) ratio implying redistribution of lower extremity flow to favor uterine circulation).

	12 wks	24 wks	36 wks
UA MFV (cm/sec)	37±2	60±6	71±6
Blood volume (mls/kg)	64±4	73±4	71±3
A/B ratio	2.4±0.2	1.9±0.1	1.7±0.1
UA/CI MFV ratio	3.7±1.0	4.2±0.4	5.2±0.5

Thus, blood volume expansion, decreased uterine artery vasular resistance and redistribution of lower extremity flow to favor the uterine circulation may contribute to increased uterine artery MFV, blood flow and the preservation of normal birth weight at high altitude. Supported by NIH 14985, NIH 000681, NSF BSN-8903554.

Maternal O_2 transport and fetal growth in Colorado, Peruvian and Tibetan populations. L.G. MOORE, University of Colorado at Denver, Denver, CO 80202.

Human populations have lived at high altitude for periods of time ranging from <100 yrs in Colorado to approx 10,000 yrs in Peru and perhaps more than 20,000 years in Tibet. To test the hypothesis that the populations longest resident at high altitude are better adapted due to superior abilities to transport and/or utilize O_2, we conducted studies in residents of Leadville, CO (3100 m), Cerro de Pasco, Peru (4300 m) and Lhasa, Tibet, China (3658 m). Based on previous data showing that reductions in birth weight occur at high altitude and are associated with increased infant mortality, our criterion for assessing adaptation was preservation of birth weight close to the sea level 3400 g standard. Average weights of babies born to 44 women studied in Leadville (3186 ± 70 g) and 20 women in Peru (2920± 90 g) were consistent with the magnitude of altitude increase but babies born to 15 Tibetan women were heavier than their altitude-counterparts (3307± 110 g). The pregnant women in all 3 groups increased their ventilation but elevated levels of arterial O_2 saturation were only present in the Peruvian and Colorado samples. Maternal ventilation in the third trimester correlated with infant birth weight in Leadville and Peru. A fall in hemoglobin concentration acted to reduce calculated arterial O_2 content in the pregnant compared to nonpregnant state but the fall in O_2 content was offset by the ventilation-induced rise in O_2 saturation in the Colorado and Peruvian samples. The Tibetan women exhibited a greater decrease in hemoglobin and calculated arterial O_2 content (ΔC_aO_2 = 2.6 mls O_2%) than the Leadville or Peru women (ΔC_aO_2 = 1.1 and 0.2 mls O_2% respectively). Assessment of uterine blood flow in the Tibetan pregnant women (using Doppler ultrasound) revealed high levels of uterine artery mean blood flow velocity and a positive correlation between birth weight and the uterine artery/common iliac artery mean flow velocity ratio (r = .69). Redistribution of lower extremity blood flow to favor the uterine circulation may have acted to offset the fall in arterial O_2 content and augment uterine O_2 delivery in the Tibetan women. Thus the limited data available lent support to the hypothesis that the longest resident high altitude population may have become better adapted (as judged by less fetal growth retardation) and may utilize a maternal O_2 transport strategy reliant upon increased uterine blood flow rather than arterial O_2 content.

Am J Phy. Anthro 78: 274, 1989

AMERICAN JOURNAL OF HUMAN BIOLOGY 2:627–637 (1990)

Maternal O_2 Transport and Fetal Growth in Colorado, Peru, and Tibet High-Altitude Residents

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ABSTRACT Human populations have lived at high altitudes for lengths of time which are likely to be shortest in Colorado, intermediate in Peru, and longest in Tibet. We hypothesized that the longest-resident high-altitude populations have become better adapted than shorter-resident groups as a result of superior abilities to transport and/or utilize O_2. Because birth weights are reduced at high altitude and decreased birth weight is associated with increased infant mortality, our criterion for assessing adaptation was preservation of birth weights close to values associated with the lowest mortality risk. Colorado (3,100 m) and Peru (4,300 m) birth weights averaged 3,186±70 g and 2,920±90 g respectively. A sample of 15 births from Tibet (3,658 m) weighed 3,307±110 g which was more than their altitude counterparts and close to sea-level norms. Pregnancy increased maternal ventilation at all three study sites. In Peru, the resultant elevation in arterial O_2 saturation offset the pregnancy-induced fall in hemoglobin concentration to preserve arterial O_2 content at nonpregnant levels. Arterial O_2 content decreased slightly in Colorado and more markedly in Tibet in the pregnant compared to the nonpregnant state. The Colorado and Peru women with the greatest rise in ventilation and ventilatory sensitivity to hypoxia produced the heaviest birthweight infants, suggesting that maternal arterial oxygenation was an important determinant of fetal growth. The pregnant women in Tibet did not have higher levels of arterial O_2 content than the pregnant Colorado or Peru women nor did maternal arterial O_2 content relate to birth weight in Tibet. Infant birth weight in Tibet tended to be correlated with the ratio of uterine artery to common iliac artery mean flow velocity, suggesting that redistribution of lower-extremity blood flow to favor the uterine circulation may have acted to augment uterine O_2 delivery in the Tibet women. Thus, the limited data available suggested that the Tibetans may be better adapted as judged by less fetal growth retardation and may utilize maternal O_2 transport mechanisms not reliant upon increased arterial O_2 content.

A central focus of biological anthropology is to understand the mechanisms by which populations adapt to environmental stress. Studies of newcomers and populations living permanently at high altitude have contributed much to our knowledge of the biological characteristics of high-altitude residents but our understanding of the extent to which adaptation has been achieved and the processes involved remains fragmentary. One difficulty involves the meaning of the term *adaptation*. In the Darwinian sense, an *adaptation* refers to the ability to live and reproduce successfully in a given environment (Dobzhansky, 1968). Yet often the term is used to refer simply to the presence of a trait that is presumed to benefit the organism; rarely do we know whether or not actual benefit exists (Fischer, 1985). Another problem concerns the identification of genetic factors involved. While the response need not be genetic to be considered an adaptation, at least some degree of genetic involvement is necessary for natural selection to increase the frequency or result in fixation of

Received July 12, 1989; accepted April 26, 1990.

Published 1990 by Wiley-Liss, Inc.

the trait in long-resident high-altitude groups. While some degree of genetic control has been identified for physiological traits which respond to high altitude (Collins et al., 1978; Cruz et al., 1980; Mueller et al., 1980), the genetic involvement is typically complex. A final issue concerns the selection of a suitable study design. An approach that has been used successfully involves the comparison of groups living at a single high-altitude location which differ with respect to particular characteristics (Leonard et al., 1990; Greksa, 1990). Another approach has been to compare populations living in South American and Himalayan high-altitude regions (Beall et al., 1990; Schoene et al., 1990; Winslow et al., 1990). We chose a variant of this latter approach, extending the comparison to include high-altitude residents of Colorado, Peru, and Tibet.

Based on the likelihood that the processes of adaptation are time-dependent, it can be hypothesized that the longest-resident high-altitude populations are better adapted to high altitude than shorter-resident groups as a result of superior abilities to transport and/or utilize O_2. Humans are likely to have lived permanently at high altitude in Colorado for only a short (<100 years) period of time, affording the opportunity to examine the effects of high altitude in the absence of selective, multi-generational processes. The occupation of Peru is likely to have been for an intermediate length of time (at least 10,000 years) whereas humans have lived on the Tibetan Plateau since the Upper Paleolithic (≥25,000 years ago) Zhimin et al., 1982; Dennell et al., 1988). However, until the necessary archaeological and genetic comparisons are performed, there is no certainty that the contemporary residents of Peru or Tibet are the genetic descendents of the earlier populations.

Our criterion for assessing adaptation was preservation of birth weights close to values associated with the lowest mortality risk. Pregnancy poses an adaptive challenge during which one generation must successfully reproduce the next. Under the conditions of reduced O_2 availability at high altitude, the question arises as to how well and by what mechanisms the maternal O_2 transport system meets the increased O_2 demands of pregnancy. It is well known that infant birth weights are reduced at high altitude (Lichty et al., 1957; McClung, 1969). Some evidence supports the possibility that there is less mortality risk associated with low birth weight at high compared to low altitude (Beall 1981; Unger et al., 1988). However, this does not mean that is is advantageous to be small at high altitude since lower birth weight infants still experience a greater mortality risk than do normal birth weight babies. Thus, the reduced infant birth weights at high altitude and the increase in infant mortality associated with decreased birth weight at all altitudes (McCormick, 1985; Unger et al., 1988) may be interpreted as evidence of incomplete adaptation to high altitude. Whereas reductions in birth weight at high altitude have been previously described in North and South America, no data to our knowledge exist on infant birth weight from Tibet (McCullough et al., 1977; Moore and Regensteiner, 1983; Yip, 1987). Therefore, our approach was to obtain birth weights for a sample of Tibet babies and to compare these birth weights with values which we and others obtained previously in Colorado and Peru. Because we have previously shown that characteristics of maternal O_2 transport during pregnancy at high altitude relate to infant birth weight (Moore et al., 1982a,b, 1986), measurements of maternal arterial O_2 content and uterine artery flow velocity were made in the Tibet women and compared with data obtained previously from Colorado and Peru.

MATERIALS AND METHODS

Subjects

Forty-four residents of Leadville, Colorado (elev 3,100 m), 21 residents of Cerro de Pasco, Peru (4,300 m), and 15 residents of Lhasa, Tibet, China (elev 3,658 m), were studied between weeks 36 and 37 of pregnancy with their informed consent. In Colorado and Peru, the same women were studied while pregnant and again 4 months postpartum for a measurement in the nonpregnant state. In Tibet, postpartum studies have not been completed and hence data are reported from a group of nine different, nonpregnant women. All the women were judged healthy by local physicians and were receiving prenatal care at local health care facilities. Effort was made to contact all women residing at the study site who were pregnant at the time of the study. Over 90% of the women contacted in Peru or Tibet participated and complete studies were obtained in 60% of the Colorado women.

Maternal age, height, weight, reproduc-

tive histories, and years residence at high altitude for the subjects at the three study sites are reported in Table 1. The Colorado women were taller and heavier than the Peru or Tibet women and the Tibet women had fewer previous births than the other subjects. None of the Peru or Tibet women smoked and, of the Colorado women, 35 were nonsmokers as judged by personal history and measured carboxyhemoglobin levels. All the Peru and Tibet women had been born and had lived their entire lives at or above their current altitude of residence (Table 1). In Peru, most women had some parents or grandparents from the Huanuco region (elev. 2,000–3,000 m) or northcentral Peru. In Tibet, all the subjects' parents and previous generations had lived at or above the elevation of Lhasa. In Leadville, the average length of residence at high altitude was 7±1 years and all but seven had been born at low altitudes. All Leadville women but none of the Peru or Tibet women took prenatal vitamins.

Protocol

Studies were performed at the Leadville Medical Center in Colorado (elev 3,100 m), the High Altitude Research Laboratory in Cerro de Pasco, Peru (elev 4,300 m), and the Tibet Institute of Medical Sciences in Lhasa, Tibet (elev 3,658 m). Measurements were made in resting subjects who had come to the laboratory after a 2–4 hour fast. Height and weight were measured by using conventional anthropometric techniques (Weiner and Lourie, 1981).

While seated comfortably in a chair and breathing room air through a respiratory valve (Koegel Y Valve, San Antonio, TX) with a nose-clip in place, end-tidal gas tensions were monitored in the Peru and Tibet subjects by using a fuel cell O_2 analyzer (Model 101, Applied Technical Products, Denver, CO) and a CO_2 infrared analyzer (Model LB2, Sensor-Medics, Anaheim, CA) previously calibrated with gases analyzed by the microscholander technique. After 3–5 minutes or once stable end-tidal gas values were achieved, minute ventilation was measured in the Colorado and Peru subjects by collecting the expired air into a recording 13 liter Collins spirometer (Braintree, MA) or, in the case of the Tibet women, into a dry gas meter (Parkinson Cowan) for the measurement of expired volume. Arterial O_2 saturation was monitored by using an ear oximeter (Model 47201A, Hewlett Packard, Waltham, MA) in the Colorado, Peru, and Tibet women. The electrical signals from the fuel cell O_2 analyzer, ear oximeter, CO_2 infrared analyzer, and dry gas meter were recorded by using strip-chart recorders.

In Tibet, Doppler Ultrasound was used to insonate the major vessels supplying blood flow to the uterus while the subject rested quietly in the left lateral supine position by using a Doppler instrument developed in the CVP Laboratory in Denver (Reeves et al., 1985). The Doppler instrument was used in pulsed mode with either a 3.25 or 5.0 mHz transducer 6 mm in diameter with a 4 cycle transmit burst. Both the mean flow velocity and the distribution of flow velocities were measured continuously throughout the cardiac cycle, recorded on magnetic cassette tape and stored for later analysis after digitizing at a 100 Hz sample rate for computer analysis (Nova General 1200). Doppler recordings were obtained from the external iliac, common iliac, and uterine arteries. After positioning the Doppler transducer gently on the skin, the range depth and angle of insonation were adjusted to obtain a maxi-

TABLE 1. Sample characteristics (Mean ± SEM)

	Leadville, Colorado	Cerro de Pasco, Peru	Lhasa Tibet	
			Preg.	Nonpreg.
Sample size	44	21	15	9
Wk pregnant	36 ± 1	36 ± 0	37 ± 1	—
Age, years	27 ± 6	27 ± 1	24 ± 1	20 ± 1
Height, cm	164 ± 1	148 ± 1	158 ± 1	154 ± 2
Weight, kg	73 ± 2[1]	61 ± 2[1]	58 ± 2	49 ± 2
Parity, No.	2.2 ± 0.2	2.0 ± 0.4	0.5 ± 0.1	0 ± 0
Years at altitude	7 ± 1	27 ± 1	24 ± 1	20 ± 1

[1]Maternal weight listed is at time of study. Maternal weights 4 months postpartum were 65 ± 2 and 53 ± 2 kg in Colorado and Peru, respectively.

mal visual and auditory velocity signal. In prior studies in which simultaneous imaging was used (Accuson 128), we were able routinely to insonate the common iliac and uterine vessels at an angle of 30 degrees. We therefore assumed a 30 degree angle for the calculation of the common iliac and uterine artery mean flow velocity measurements reported here.

Blood was withdrawn from the antecubital vein in the Leadville and Peru women to measure hemoglobin in the pregnant and postpartum states for spectrophotometric analysis by using the cyanmethemoglobin technique. In Tibet, hemoglobin was measured in resting subjects in duplicate from blood samples obtained without squeezing by finger stick using a photometer (HemoCue Photometer, Aktiebolaget Leo, Helsingburg, Sweden). In a comparison of 28 hemoglobin values ranging from 0 to 22 g %, measurements obtained using the photometer agreed to within 0.2±0.1 g % of values obtained spectrophotometrically. Arterial O_2 content was calculated as the product of the O_2 carrying-capacity (hemoglobin concentration × 1.36) and the fractional arterial O_2 saturation. O_2 carrying-capacity was corrected for the carboxyhemoglobin levels measured in the Leadville subjects. No such correction was performed in the Peru or Tibet women since none of the subjects were smokers.

Statistics

The 90% tolerance limits (Sokal and Rohlf, 1981) were calculated for the relationship between infant birth weight and altitude by using previously published data. Comparisons between measurements in the pregnant and nonpregnant states were performed with paired t-tests in Leadville and Peru and two sample t-tests in Tibet. Values were compared among the Colorado, Peru, and Tibet women by using one-way analysis of variance with SNK or Fisher PLSD multiple comparisons to test for pairwise differences. Linear regression and correlation techniques were used to examine relationships between variables. Results were considered significant when $P<0.05$. Data are reported as means±SE.

RESULTS

All infants were full-term as assessed from the date of the last menstrual period (Table 2) and, in Colorado and Peru, from clinical exam (39.6±0.2 wk and 40.0±0.1 wk respectively). The Tibet babies weighed more than the Colorado or Peru babies (Table 2). In order to assess birth weight in relation to altitude, the average weights were plotted against altitude and compared to published data from North and South America (Fig. 1). The birth weights from the Colorado and Peru samples fell within the 90% tolerance limits calculated for their respective elevations but the birth weights of the Tibet babies were greater than their altitude counterparts (Fig. 1). Newborn lengths were similar at the three study sites (Table 2).

Pregnancy raised maternal ventilation in Colorado, Peru, and Tibet (Table 2). Arterial O_2 saturation increased with pregnancy in Colorado and Peru but values were similar in the pregnant and nonpregnant Tibet women. Hemoglobin concentration was lower in the pregnant than the nonpregnant women at all three study sites (Table 2). In Peru, the rise in arterial O_2 saturation with pregnancy compensated for the fall in hemoglobin concentration to preserve arterial O_2 content at nonpregnant values (Fig. 2). Arterial O_2 content was lower in the pregnant Colorado and Tibet women compared to values observed in the nonpregnant state Fig. 2, Table 2). The difference between the arterial O_2 content values measured in the pregnant and nonpregnant states was greater in Tibet (−2.73±0.62 ml %) than in Colorado or Peru (−1.34±0.43 and −0.03± 0.46 ml % respectively, both $P<0.05$). Uterine artery and common iliac artery mean flow velocity were measured in a subset of the Tibet women (Table 2). The uterine artery mean flow velocity values were increased six-fold compared to values measured at low altitude in the nonpregnant state (Palmer et al., 1990). Since the uterine arteries constitute a major source of uterine blood supply, the increased uterine artery mean flow velocity in the Tibet pregnant women likely raised uterine O_2 blood flow and O_2 delivery.

In Colorado, the women producing heavier birth weight infants were characterized by higher arterial O_2 contents which in turn resulted from higher levels of minute ventilation and a lesser fall in hemoglobin with pregnancy (Moore et al., 1982a,b). In Peru, the women with the greatest increase in hypoxic ventilatory response had the greatest rise in ventilation and arterial O_2 satura-

TABLE 2. Infant and maternal characteristics (mean ± SEM)[1]

	Leadville, Colorado	Cerro de Pasco, Peru	Lhasa, Tibet	*P* value
Infant				
Birth weight, g	3,199 ± 74	2,923 ± 90	3,307 ± 110	<.05
Gestational age, wk	40.2 ± 0.4	39.7 ± 0.3	40.5 ± 0.0	NS
Length, cm	49.7 ± 0.8	49.1 ± 0.5	48.7 ± 1.2	NS
Maternal				
Ventilation,	9.4 ± 0.5	9.7 ± 0.4	9.9 ± 0.5	NS
liters BTPS/min	11.8 ± 0.4*	12.0 ± 0.7*	11.3 ± 0.3+	NS
Nonpg				
Preg				
End-tidal	25 ± 1[2]	26 ± 1	28 ± 1	NS
PCO_2, mmHG	29 ± 1[2]*	31 ± 1*	31 ± 1+	NS
Nonpg				
Preg				
Arterial O_2	92.1 ± 0.2	82.9 ± 1.2	89.[illegible] ± 0.7	<0.01
saturation, %	93.4 ± 0.3*	87.8 ± 0.4*	89.7 ± 0.4	<0.01
Nonpg				
Preg				
Hemoglobin,	14.8 ± 0.2	14.0 ± 0.4	14.9 ± 0.2	NS
g/100 ml	13.2 ± 0.2*	13.2 ± 0.3*	12.7 ± 0.3+	NS
Nonpg				
Preg				
Arterial O_2	17.9 ± 0.3	15.8 ± 0.4	18.1 ± 0.3	<0.01
Content, ml%	16.6 ± 0.3*	15.7 ± 0.4	15.5 ± 0.3+	<0.05
Nonpg				
Preg				
Uterine a	—	—	—	
MFV, cm/sec	—	—	48 ± 2	
Nonpg				
Preg				
Uterin a:	—	—	—	
Cmn iliac a	—	—	4.6 ± 0.5	
MFV ratio				
Nonpg				
Preg				

[1]Abbreviations: MFV = mean flow velocity. *P* values indicate comparison between three groups in either the pregnant or the nonpregnant condition using one-way ANOVA. See text for indication of significant pairwise differences.
[2]Arterialized PCO_2.
*Comparison between nonpregnant and pregnant subjects using paired t-test, $P < 0.05$.
+Comparison between nonpregnant and pregnant subjects using unpaired t-test, $P < 0.05$.

tion and produced the heaviest birth weight infants (Moore et al., 1986). In Tibet, arterial O_2 content was not related to infant birth weight ($r = 0.29$, P = NS). Given that the Tibet women did not have higher levels of arterial O_2 content than the Peru or the Colorado women (Fig. 2), the higher infant birth weights observed in Tibet were not due to an increased arterial O_2 content. Either the differences in infant birth weight among the three samples were unrelated to maternal O_2 transport or some factor other than arterial O_2 content acted to raise uterine O_2 delivery in the Tibet women. Since uterine O_2 delivery is the product of arterial O_2 content and uterine blood flow, variation in uterine blood flow may also be related to birth weight. Preliminary measurements of uterine artery mean flow velocity in nine women and common iliac mean flow velocity in six Tibet women were obtained (Table 2). The uterine artery mean flow velocity was unrelated to birth weight but the ratio of the uterine artery to common iliac artery mean flow velocity tended to be positively correlated with birth weight (Fig. 3).

DISCUSSION

The results of the studies presented here suggested that babies born at high altitude in Tibet weighed more than babies born at high altitude in Colorado or Peru. In addition, measurements in small numbers of pregnant women suggested that the effects of pregnancy on maternal arterial O_2 content and the relationship between characteristics

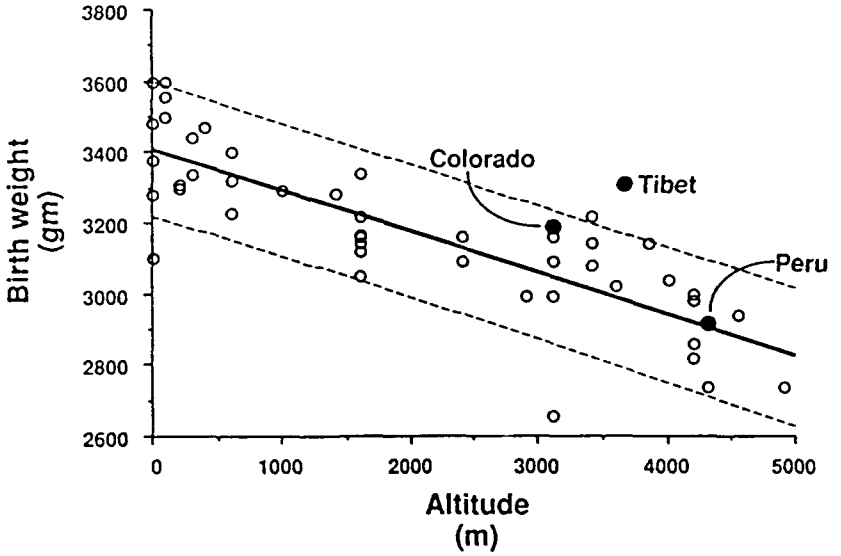

Fig. 1. Mean birth weights reported from previously published studies in North and South America (open circles, see ref. in Moore and Regensteiner, 1983) are shown with the upper and lower 90% confidence limits (dotted lines). The average birth weights from the Colorado and Peru samples (filled circles) fall within the 90% confidence limits whereas the Tibet birth weights are higher than previously reported values.

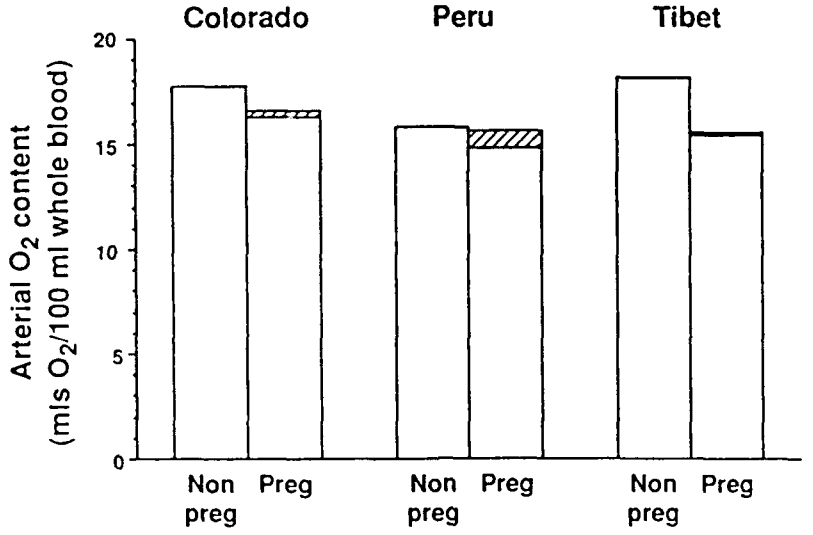

Fig. 2. Arterial O_2 content was calculated from the measured hemoglobin concentration and arterial O_2 saturation. The hatched area represents the increase in arterial O_2 content due to the rise in arterial O_2 saturation from the nonpregnant to the pregnant state. The same women were studied while pregnant (wk 36–37) and again 4 months postpartum in Colorado and Peru whereas different women were studied at wk 36–37 of pregnancy and in the nonpregnant state in Tibet.

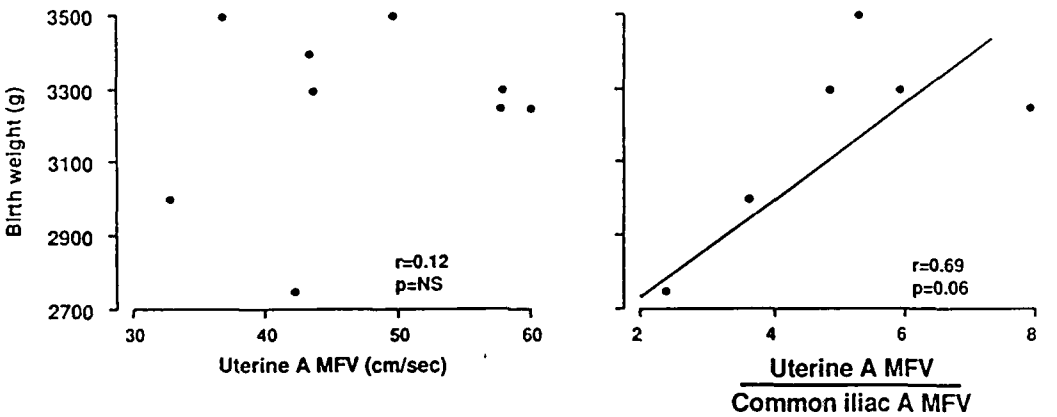

Fig. 3. Doppler ultrasound was used to obtain mean blood flow velocity (MFV) measurements for the uterine artery in nine of the Tibet women and the ratio of uterine artery to common iliac artery mean flow velocity in six of the Tibet pregnant women. Infant birth weight was not related to the uterine artery MFV but tended ($P=0.06$) to be correlated positively with an increased ratio of uterine artery to common iliac artery MFV, suggesting that redistribution of lower extremity blood flow may have favored the uterine circulation in pregnancies producing heavier birth weight offspring.

of maternal O_2 transport and infant birth weight may differ among the three study sites.

1. Birth weight comparisons

The Tibet babies weighed more than the Colorado or Peru infants when either the absolute birth weights or the birth weights in relation to altitude were examined. Since gestational ages were similar at the three locations, the heavier birth weights in Tibet suggested that differences in fetal growth rather than length of gestation were responsible. No data on infant birth weight to our knowledge have been published from Tibet or elsewhere in the Himalayas but persons in Lhasa commonly express the opinion that Tibetan babies weigh more than Han ("Chinese") babies born there. We measured birth weights in a small sample of Han babies and found that their weights were similar to values observed at similar elevations elsewhere and that the Han infants were significantly lighter than the Tibetan births (Zhoma et al., 1989). Given that all babies born in Lhasa were not large, it appeared unlikely that the heavier birth weights of the Tibet babies resulted from a consistent overestimation of birth weight.

The birth weight data obtained were consistent with the study hypothesis insofar as the Tibet babies were heavier than the Colorado or Peru births but inconsistent insofar as the Peru birth weights were not intermediate between the Colorado and Tibet values. Previous comparisons have revealed that birth weights at a given elevation are similar in North and South America (McCullough et al., 1977). However, most of the elevations at which persons reside in South America are higher than in North America. In addition, the North American data come from entire populations whereas the information from South America comes from that subset giving birth in hospitals. When carefully controlled comparisons have been made at a single elevation, Amerindian women produce heavier birth weight offspring than do European women (Haas et al., 1980a,b). However, the present as well as previous studies were not able to determine whether babies born to the longer-resident groups were protected from altitude-associated fetal growth retardation or whether population differences unrelated to altitude were responsible for the heavier birth weights observed.

2. Effects of pregnancy on maternal O_2 transport

The maternal O_2 transport system undergoes profound alterations during pregnancy. At low altitude, increased uterine O_2 delivery with advancing gestation is met principally through increased uterine blood flow. Increased maternal ventilation does not

raise arterial O_2 saturation since values are already maximal in the nonpregnant state at low altitude. Under circumstances of arterial O_2 desaturation, increased maternal ventilation raises arterial O_2 saturation. Thus, increased maternal ventilation raised arterial O_2 saturation in Colorado and Peru. It is not clear why arterial O_2 saturation was not higher in the pregnant compared to the nonpregnant Tibet women. The pregnant women in Tibet had arterial O_2 saturation values that were similar to those observed in normal Tibetan young men in Lhasa (Sun et al., 1988), suggesting that the pregnant women had lower values than expected. A widened alveolar-arterial O_2 gradient occurs in pregnancy (Awe et al., 1979) and may act to reduce arterial O_2 saturation. That the increase in arterial O_2 saturation was greater in Peru was consistent with its higher altitude. Above 4,000 m, the arterial PO_2 and O_2 saturation values are located on the steep part of the hemoglobin-O_2 dissociation curve with the result that a given rise in arterial PO_2 produces a greater increase in arterial O_2 saturation than at lower elevations. In Peru, the increased arterial O_2 saturation was sufficient to offset the modest fall in hemoglobin concentration to preserve arterial O_2 content close to nonpregnant values. In Colorado and Tibet, the rise in arterial O_2 saturation was insufficient to compensate for the lower hemoglobin with the result that arterial O_2 content was slightly decreased in the pregnant compared with the nonpregnant state in Colorado and more markedly lower in the pregnant than in the nonpregnant women in Tibet.

The greater difference in arterial O_2 content between the pregnant and nonpregnant states observed in Tibet than that seen in Colorado or Peru women probably did not reflect differences in measurement techniques. The same investigators, instruments, and study techniques were used at the three locations. Differences in study design, however, existed insofar as the same women were studied in the pregnant and nonpregnant states in Colorado and Peru but different groups of women were studied in Tibet. Therefore, the greater difference in arterial O_2 content in Tibet may have been due to differences between the two groups unrelated to the effects of pregnancy. Alternatively, depletion of iron stores may have occurred postpartum in the Colorado and Peru women, thereby resulting in lower values and less difference between the pregnant and nonpregnant states. However, all the Colorado and most of the Peru women received iron supplementation postpartum and we did not find an increase in hemoglobin between 4 months postpartum and 1–2 years postpartum in the Leadville sample; nor did the hemoglobin values measured postpartum in Peru differ from those obtained in a sample of not-previously pregnant women (Moore, unpublished observations). Another possibility was that the greater difference in arterial O_2 content between the pregnant and nonpregnant states in the Tibet women was real and reflected lower hemoglobin values due to a greater increase in plasma volume. An association between lower maternal hemoglobin and heavier birth weights has been observed previously at high altitude (Haas et al., 1980a,b). Hemoglobin concentration normally falls with pregnancy due to a greater expansion of plasma volume than the increment in red cell mass (Chesley, 1972). The increase in plasma volume is likely important for maintaining high uterine perfusion insofar as low plasma volume has been associated with reduced birth weights and poor pregnancy outcome in numerous studies at low altitude (Hytten, 1985). If so, there is a dilemma with pregnancy; either hemoglobin concentration and blood O_2 carrying-capacity are maintained or blood volume expands and hemoglobin concentration is reduced. Increased uterine blood flow during pregnancy is attributable in approximately equal proportion to an increased diameter of vessels supplying the uterus and to an increase in the average speed with which the blood is flowing through the uterine arteries (mean flow velocity). The high uterine artery mean flow velocity values from Tibet were therefore likely to have indicated an increase in uterine blood flow which, in turn, was likely to have been sufficient to offset the reduction in arterial O_2 content and yield a net increase in uterine O_2 delivery. If so, it would appear that the Tibet women have elected a strategy of increasing uterine perfusion rather than blood O_2 carrying-capacity for raising uterine O_2 delivery.

3. Relationships between characteristics of maternal O_2 transport and infant birth weight

The well-known reduction in birth weight at high altitude and under circumstances in which maternal O_2 transport is limited due

to cyanotic congenital heart disease, severe anemia, or cigarette smoking (Ueland et al., 1972; Miller and Merritt, 1979; Abel, 1980) suggest that fetal O_2 supply at high altitude is insufficient in at least some cases. The studies reported here were concerned with the possibility that decreased uterine O_2 delivery contributed to the fetal growth retardation observed. A decrease in uterine O_2 delivery could be due either to a fall in arterial O_2 content or a reduction in uterine blood flow. In our previous studies in Colorado and Peru, we have shown that factors determining maternal arterial O_2 content were related to infant birth weight (Moore et al., 1982b, 1986). The women with the greatest rise in ventilation and least fall in hemoglobin (Colorado) and the greatest rise in ventilatory sensitivity to hypoxia (Peru) produced the heaviest birth weight infants, suggesting that maternal arterial oxygenation may be an important determinant of fetal growth. However, the pregnant women in Tibet did not maintain their arterial O_2 content at levels present in nonpregnant subjects due to a reduction in hemoglobin concentration. It would appear that the heavier birth weights seen in Tibet were unrelated to maternal O_2 transport or that some factor other than arterial O_2 content was responsible for raising uterine O_2 delivery.

Uterine blood flow is likely to be the major determinant of near-term increases in fetal O_2 supply since maternal arterial O_2 content changes little in the final months of pregnancy. In the past, uterine blood flow has been difficult to measure given the complexity of the uterine circulation and ethical constraints limiting invasive techniques. Recently, the use of Doppler ultrasound has become widespread as a safe, noninvasive method for characterizing velocity waveforms in uteroplacental vessels (Giles and Trudinger, 1986). Studies at low altitude support an association between reduced uteroplacental perfusion and maternal complications of pregnancy associated with fetal growth retardation (Lunnell et al., 1982)

Since fetal growth retardation at high altitude is thought to occur in the final 6–8 wk of gestation (Unger et al., 1988), we hypothesized that infant birth weight would be related to late-pregnancy uterine blood flow. We used uterine artery mean flow velocity as an index of uterine blood flow on the basis that volumetric flow is the product of mean flow velocity and vessel cross-sectional area. The investigational Doppler available to us had a unique signal-processing capability that permitted the display of the mean flow velocity throughout the cardiac cycle. We had previously observed that increases in uterine artery cross-sectional area were complete by wk 20 whereas mean flow velocity continued to rise until term (Palmer et al., 1990) and therefore reasoned that mean flow velocity was likely to be the major determinant of uterine artery blood flow late in pregnancy. The data obtained in the present study did not support the hypothesis insofar as there was no association between uterine artery mean flow velocity and infant birth weight. The studies were limited insofar as uterine artery mean flow velocity was measured in only nine women, no information was obtained concerning vessel cross-sectional area, and the angle of insonation was not known with great precision. It was not possible to measure uterine artery diameter with the equipment available in Tibet. An angle of 30 degrees was assumed for the calculations presented here on the basis of our previous studies (Palmer et al., 1990) but we had no way of knowing whether the same angle was obtained in all women. On the basis that the ratio of the uterine artery to the common iliac artery mean flow velocity provided an index of the proportion of lower extremity flow that was directed toward the uterus and that this ratio was independent of angle if the same angle was obtained for both vessels, we examined the relationship between the uterine artery to common iliac artery mean flow velocity ratio and infant birth weight. In the six subjects in whom measurements were available, infant birth weight was more strongly associated with the ratio of uterine artery to common iliac mean flow velocity than with the uterine artery mean flow velocity alone but the correlation achieved only borderline levels of statistical significance. Further studies are required in larger numbers of subjects to determine whether redistribution of lower-extremity blood flow to favor the uterine circulation is likely to have increased uterine O_2 delivery and infant birth weight in the Tibet women. Similar measurements from Colorado and Peru are also needed to determine whether the heavier birth weights observed in Tibet related to differences in uterine O_2 delivery.

In summary, we observed that babies born

at high altitude in Tibet weighed more than babies born at high altitude in Colorado or Peru. Measurements in small numbers of pregnant women suggested that the effects of pregnancy on maternal arterial O_2 content and the relationship between characteristics of maternal O_2 transport and infant birth weight may differ among the three study sites. To simplify, the Colorado and Peru women appeared to emphasize preservation of arterial O_2 content whereas the Tibet women appeared reliant upon increased uterine blood flow rather than arterial O_2 content. Further studies are required with larger numbers of subjects to determine whether selection has taken place for characteristics of maternal O_2 transport which raise uterine O_2 delivery and minimize fetal growth retardation at high altitude.

ACKNOWLEDGMENTS

These studies were made possible by assistance from numerous investigators. In chronological order, Drs. Bob Grover, Jack Reeves, Sharon Rounds, Dennis Jahnigen, Choclo Monge, Juan D'Brot, Ovido Chumbe, Shinfu Sun, Tarshi Droma, and Stacy Zamudio provided invaluable and expert advice. Special thanks are owed the subjects whose willingness to participate truly made the studies possible. Grant support was obtained from the National Foundation-March of Dimes (6-169), the American and Colorado Heart Associations (80-837), NIH-CHD 000681 and NIH-HLBI 14985.

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Blood volu ne expansion and pregnancy outcome in high altitude pregnancy. S.A. ZAMUDIO, T.S. DROMA, S.K. PALMER, J. BERMAN, T.E. DAHMS, R.E. McCULLOUGH, R.G. McCULLOUGH and L.G.MOORE; University of Colorado at Denver and Health Sciences Ctr, Denver, CO 80262.

The incidence of pregnancy-induced hypertension (PIH; syn. toxemia, preeclampsia) and low birth weight (LBW) are increased at high versus low altitude. PIH and LBW present risks to maternal/fetal survival and may be indicative of adaptive stress related to the reduced oxygen availability of high altitude. Our approach has been to determine whether characteristics of maternal oxygen transport are related to the occurrence of PIH and LBW.

Sea level studies have shown that blood volume expansion (particularly plasma) relates to birth weight, and is lower in PIH than normal pregnancy. We hypothesized that higher incidence of LBW and PIH at high altitude is due, in part, to lower blood volume in pregnancy. Blood volume (BV) was measured using a carbon monoxide rebreathing technique in 39 pregnant (PG) Leadville women and 4 months postpartum (NP). (* PG vs NP, $p < .05$)

	NP	12 wks	24 wks	36 wks
BV (mls)	3457	3718	4315*	4775*
BV (ml/kg)	55.2	61.2	65.5*	65.5*
PV (mls)	1932	2197	2639*	2936*
PV (ml/kg)	30.8	36.2*	40.1*	40.3*

There was a 38% increase in absolute blood volume, accounted for by a 52% increase in plasma volume (PV) and a 21% increase in red cell mass. Blood volume normalized for body weight increased 19% by 24 weeks. While the pattern of volume expansion agreed with normal literature values, these high altitude data are 18% lower than sea level averages.

Birth weight correlated with third trimester absolute blood volume in normal women ($r=.55$, $p< .01$). Women with PIH ($n=9$) had lower plasma volumes (ml/kg) throughout pregnancy and lower blood volume at weeks 24 and 36 ($p< .05$). Absolute blood volumes were not different. Infants of PIH versus normal mothers were not significantly smaller (2985 vs. 3197 grams).

We conclude that blood volume attained during pregnancy may be an important factor influencing maternal well-being and fetal growth. Further research is needed to identify the determinants of blood volume expansion during pregnancy and the extent to which variation in blood volume expansion as well as other characteristics influencing maternal oxygen transport differ between long- vs. short-term resident populations at high altitude. Grant support: NSF BNS-8903554, BNS 8919645, NIH-HL14985 & HD000681.

SEVENTH INTERNATIONAL HYPOXIA SYMPOSIUM
McMASTER UNIVERSITY, THE ARCTIC INSTITUTE OF NORTH AMERICA

FEBRUARY 26 - MARCH 2, 1991

CIRCULATORY CHANGES IN NORMAL VERSUS HYPERTENSIVE PREGNANCY AT HIGH ALTITUDE.

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Women with pregnancy-induced hypertension (PIH) have altered vascular reactivity and low blood volume (BV), implying an abnormal vascular response to pregnancy. We have observed an increased incidence of PIH at high compared with low altitude. To characterize vascular responses to pregnancy, we studied 34 residents at 3100m while pregnant and postpartum. (* $p<.05$)

	MAP	BV	PV	UA/CI	EI/CI	MAP/UA
Norm	84	65.5	40.3	4.6	.78	1.46
PIH	99*	56.5*	34.5*	3.3*	.92*	1.88*

At week 36, BV (ml/kg, CO rebreathing) had increased 19% in 25 normal but not in 9 PIH women. Values in normals were 15% below reported sea-level norms during and after pregnancy. Uterine a. mean flow velocity (MFV, Doppler) divided by common iliac a. MFV (UA/CI) was higher, and external iliac a. MFV divided by CI (EI/CI) was lower in normal compared to PIH women. Normal women thus distributed a greater proportion of flow to the UA than women with PIH. Higher MAP in PIH women raised the UA resistance index (MAP/UA), possibly limiting redistribution of flow from other vessels. Study results suggested that an abnormal vascular response to pregnancy may limit BV expansion and predispose some women to develop PIH.

NSF BNS-8903554, NIH-HL14985 & HD000681.

Oxygen transport during steady-state submaximal exercise in chronic hypoxia

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high altitude; acclimatization; hypoxia; oxygen content; cardiac output; leg blood flow; blood volume; plasma norepinephrine

ACCLIMATIZATION to moderate altitudes of 3,000–4,000 m involves adaptations in O_2 transport, particularly during exercise, that are poorly understood. For example, increases in hemoglobin concentration and arterial O_2 saturation are offset by reductions in cardiac output and stroke volume (SV) (2, 5, 7, 13, 15, 18, 24, 29, 30). The net result is that O_2 delivery during submaximal exercise does not increase with acclimatization. Similar findings have been obtained with coronary blood flow during exercise at 3,100 m (7), as well as in exercising limb blood flow at 4,300 m (3). One of the permeating concepts in all these studies of acclimatization is that the reduction in blood flow acts to maintain a constant level of O_2 transport.

The reductions in cardiac output and leg blood flow (LBF) with acclimatization have been believed to be the result of a reduction in plasma volume seen at altitude (1, 2). This explanation is not consistent with the findings of several studies that failed to demonstrate an increase in cardiac output despite manipulation of plasma volume (2, 13). In addition, long-term residents of moderate altitude have been shown to have an increase in cardiac output after 10 days at sea level (SL) despite no significant change in total blood volume (12). Thus mechanisms in addition to, or other than, blood volume may be important in the modulation of blood flow with acclimatization (3, 29).

Measurements of mean systemic arterial pressure and systemic vascular resistance during exercise have demonstrated significant elevations with residence at high altitude (3, 7, 24, 29, 30). The cause for these elevations has not been determined, but heightened sympathetic nervous system activity, as suggested by increased plasma norepinephrine (NE) levels (21), may have an important role. Sympathetically mediated arterial vasoconstriction could result in reductions in both local and systemic blood flow, thereby preventing an increase in O_2 transport with acclimatization despite the improvement in arterial O_2 content.

The purpose of this study was to investigate the effect of acclimatization at 4,300 m on both total body and leg O_2 transport during more prolonged steady-state exercise. In addition, the relative importance of blood volume and arterial vascular resistance on the blood flow adaptations to chronic hypoxia were determined.

Measurements of cardiac output, LBF, arterial and venous blood oxygenation, and arterial blood pressure were made at rest and repeatedly during a 45-min bout of steady-state exercise at the same absolute level of total body O_2 uptake ($\dot{V}O_2$) at SL, immediately on arrival at an altitude of 4,300 m, and after a residence of 21 days at altitude. Blood volume under resting conditions was estimated at SL and after acute and chronic exposure to altitude. Finally, plasma NE levels were obtained to evaluate a potential relationship between heightened sympathetic nervous activity and the circulatory responses during exercise with acclimatization.

METHODS

Measurements were made at rest and during steady-state exercise while subjects were breathing ambient air at SL [barometric pressure (P_B) 751 Torr, inspired P_{O_2} ($P_{I_{O_2}}$) 148 Torr], within the first 4 h of arrival at 4,300 m (P_B 463 Torr, $P_{I_{O_2}}$ 87 Torr), and after 21 days residence at altitude (P_B 461 Torr, $P_{I_{O_2}}$ 87 Torr). Studies at high altitude began 4 wk after those performed at SL. Subjects traveled by air transportation from SL to Denver, CO and slept at 1,954 m (Manitou Springs) the night before ascending to 4,300 m. Subject arrival at altitude was staged so that all subjects were studied promptly on arrival and after an equivalent period of residence at altitude. The SL studies were performed at the Geriatrics Research, Education and Clinical Center of the Palo Alto Veterans Administration Medical Center, whereas the altitude studies were performed in the United States Army, Maher Memorial Research Laboratory on the summit of Pikes Peak, CO (4,300 m, P_B 463 Torr). The design was to make measurements during high altitude hypoxia before and after acclimatization and to compare them with measurements during normoxia at SL.

Subjects. Seven males gave their informed consent for participation in the research study approved by the Human Subjects Committees of the University of Colorado Health Sciences Center, Stanford University, the University of California, Berkeley, and the US Army. The subjects averaged 23 ± 2 (SE) yr of age, 72.0 ± 1.6 kg body wt, and 11.7% body fat by hydrostatic weighing; all were residents near SL with no recent altitude exposure. Only one of the subjects was involved in regular endurance exercise training, but he had not been training vigorously for ≥1 mo before the beginning of the SL phase.

Diet. Food intake was controlled at SL and at altitude, with a food and formula diet provided in amounts sufficient to cover measured energy needs. Compliance to the dietary regimen was enforced and fluid intake at altitude was encouraged and enforced, averaging 4,854 ± 447 ml/day. Body weight was 72.0 ± 1.6 kg at SL, 73.4 ± 1.8 kg on arrival at 4,300 m, and 71 ± 1.8 kg after 21 days at high altitude.

Maximum oxygen uptake ($\dot{V}O_{2\,max}$). $\dot{V}O_{2\,max}$ was determined by the use of a progressive exercise protocol on a cycle ergometer to determine the exercise intensity to be used during the steady-state submaximal exercise study. Work load was increased 25 W every 2 min until the subject's inability to continue despite strong verbal encouragement. $\dot{V}O_{2\,max}$ was the value obtained when an increase in exercise intensity of 25 W did not result in any further increase in $\dot{V}O_2$ (i.e., a decrease, no change, or an increase <150 ml/min). This resulted in a plateau in $\dot{V}O_2$ in the majority of subjects. Measurements were made after an initial familiarization test on two separate days at SL and on days 5, 7, and 18 at 4,300 m breathing ambient air. Subjects exercised on a Warren Collins Pedal-mode electronically braked cycle ergometer, precisely calibrated for work load. Respiratory gas exchange was measured on-line by the use of standard open circuit techniques (AMETEK S-3A O_2, Beckman LB-2 CO_2 analyzers, Validyne MP 45 pressure transducer, and Fleisch no. 3 Pneumotachometer). These measurements were used to calculate $\dot{V}O_2$, CO_2 production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$). The same equipment was used for all exercise studies at SL and high altitude.

Steady-state exercise. A submaximal work load was chosen to produce a $\dot{V}O_2$ that was 50% $\dot{V}O_{2\,max}$ at SL. This same absolute $\dot{V}O_2$ was used for all steady-state exercise studies at SL, on acute ascent to 4,300 m, and after 21 days of residence at high altitude. Because $\dot{V}O_{2\,max}$ did not change between a few days of arrival and 18 days of residence at altitude, this work load represented the same $\%\dot{V}O_{2\,max}$ for both studies at high altitude, but was at a higher relative work load compared with SL.

Resting measurements were made while the subjects sat quietly in a chair for 1 h after all instrumentation had been completed. Subjects were then seated on the cycle ergometer and exercised for 45 min. Various measurements, as described below, were made after 5, 15, 30, and 45 min of exercise. All subjects were able to complete 45 min of exercise at SL and after 21 days at altitude. Two subjects were able to exercise for only 30 min on arrival.

Femoral arterial and venous catheterization. After the introduction of local xylocaine anesthesia, the femoral artery and its vein in the same leg were cannulated by the use of standard percutaneous techniques as previously described (3). A 5-Fr, 23-cm catheter (North American Medical Instrument, model 91100900) was positioned in the distal abdominal aorta. A 6-Fr thermodilution venous catheter (American Edwards Laboratories, model 93-135-6F) was passed through a femoral vein sheath to position its tip in the iliac vein ~13 cm from the skin. Both catheters were secured by a suture in the skin and a stretch bandage wrap around the upper thigh and waist over the point of insertion. The external portions of both catheters were directed laterally along the thigh to allow access for sampling during exercise. There were no significant complications from this procedure. Alternate legs were used for each testing period.

Blood measurements. Arterial and leg venous blood samples were drawn simultaneously anaerobically, over 5 s when $\dot{V}O_2$ had reached a steady state at rest and at 5, 15, 30, and 45 min during exercise. The blood samples were immediately placed on ice and were analyzed within 30 min for P_{O_2} and P_{CO_2} and pH (ABL 300, Radiometer

Copenhagen). Oxygen content, oxygen saturation, and hemoglobin (Hb) concentration were measured independently on each blood sample (OSM 3 Hemoximeter, Radiometer Copenhagen), and arterial hematocrit (Hct) was determined by the microhematocrit method. The temperatures measured at the venous catheter tip thermistor were utilized to correct blood gas tension to in vivo temperature.

Arterial blood was also obtained at rest and after 15, 30, and 45 min of exercise for the determination of plasma NE levels. These samples were analyzed with a liquid chromatography technique (10).

Hemodynamic measurements. Heart rate was determined by single-lead electrocardiographic monitoring on a Soltec recorder (model 8K22, Sun Valley, CA). Distal abdominal aortic arterial pressure was monitored at rest and throughout exercise with a fluid-filled transducer (Statham, model 23 DB) calibrated to zero pressure at 5 cm below the sternal angle (9) with phasic recordings on the Soltec recorder.

After blood sampling at rest and during exercise, cardiac output was determined by the indocyanine green dye dilution technique, with a bolus injection of dye into the iliac vein and continuous sampling of femoral arterial blood through a spectrophotometric cell (Waters D-402A densitometer and cuvette, Rochester, MN) to generate an indicator-dilution curve on the recorder. Measurements were made at rest and at ~5, 15, 30, and 45 min of exercise. The validity of each measurement was determined by the morphology of the curve as well as the consistency of the output throughout the same exercise load. If the curve morphology was considered atypical, the cardiac output determination was repeated with rezeroing of the spectrophotometer to account for any residual dye from the first injection. A volume of 0.75 ml of dye was used for the studies at SL and on arrival at high altitude, whereas the amount was reduced to 0.5 ml for the study after acclimatization (because the curves were larger due to the decline in cardiac output). Cardiac output was determined from these curves with the standard formula cardiac output = $I \times 60$ s/min/$A \times$ cal factor, where I is indicator concentration, A is area of the curve, and the cal factor is determined from a standard curve of green dye in the individual subject's blood (19). The Hamilton method was used to evaluate the descending portion of the curve before recirculation (11).

After blood sampling, iliac venous blood flow was estimated from a 10-ml bolus injection of sterile saline cooled to near 0°C through an American Edwards Laboratories—Set II (93–520) by the thermodilution technique using a cardiac output computer (American Edwards Laboratories model 9520). Measurements were made in triplicate at rest and during each sampling period during exercise. Validity of the measurements was determined by obtaining appropriate thermodilution morphology curves on the Soltec recorder with each determination. The validity and precautions used with this technique have been described previously (3, 28).

Derived hemodynamic variables. SV was calculated by dividing cardiac output by heart rate. Systemic vascular resistance was determined by dividing mean arterial pressure (MAP) by cardiac output, whereas leg vascular resistance was obtained by dividing MAP by LBF. Resistance values are expressed as peripheral resistance units (Torr · l^{-1} · min). Leg vascular conductance was determined by dividing LBF by MAP. Total body O_2 transport or delivery was the product of cardiac output × arterial O_2 content, whereas leg O_2 transport was the product of leg blood flow × arterial O_2 content.

Blood volume measurements. Blood volume was determined by the use of a modified carbon monoxide (CO) rebreathing technique. This method entailed having the subject rebreathe a 6- to 8-liter gas mixture containing >40% O_2 in N_2 with a CO_2 absorber placed in the inspired line. Venous blood samples were obtained 5 min before and 10 min after the introduction of a known volume of CO into the rebreathing circuit. Hct was measured immediately afterward, and samples were stored at 4°C for subsequent measurement of total Hb and carboxyhemoglobin (HbCO). All measurements were made by one investigator (*TED*). HbCO was measured by the use of a previously described chromatographic technique (4). Total blood volume was calculated by the formula $BV = (V\dot{C}O_{STPD}/\Delta CO/Hb_a)/[Hb]_c$, where BV is total blood volume, $V\dot{C}O_{STPD}$ is the volume of carbon monoxide (STPD) introduced into the rebreathing circuit, $\Delta CO/Hb_a$ is the change in HbCO expressed in milliliters STPD per gram of hemoglobin and $[Hb]_c$ is the total hemoglobin concentration per milliliter of whole blood. Erythrocyte (RBC) volume was obtained by multiplying the known blood volume by the post-CO Hct. Plasma volume was obtained by subtracting RBC volume from total blood volume. Blood volumes obtained by this technique in our laboratory were within 3–6% of values obtained by a ^{99}Tc-labeled RBC method. Repeated measurements with the use of CO rebreathing in five subjects revealed that the measurements were reproducible within 4.8 ± 0.9% for total blood volume, 5.6 ± 0.9% for RBC volume, and 2.4 ± 0.7% for plasma volume. All measurements of blood volume were obtained on a day before the performance of the steady-state exercise study to minimize any effects of blood sampling during these studies on the blood volume determination. Measurements of blood volume were obtained at SL and on *day 18* of residence at 4,300 m. Blood volume was not directly measured on arrival at altitude because of the urgency of performing the hemodynamic exercise study and the concern about the influence of CO on exercise performance. On arrival, blood volume was estimated from the change in Hct compared with SL, with the assumption that all blood volume changes were related to plasma volume effects.

Statistics. Values are given as means ± SE in the text, tables, and figures. Two-way analysis of variance (ANOVA) with both the Student-Newman-Keuls (SNK) and Scheffé multiple comparison tests was used to determine differences between testing periods as well as differences between various time points during exercise. $P < 0.05$ was considered statistically significant.

RESULTS

$\dot{V}O_{2\,max}$ was 3,549 ± 89 ml/min at SL, 2,694 ± 86 ml/min (76 ± 2% of SL $\dot{V}O_{2\,max}$) on *day 5* (PP-5), 2,679 ± 93

TABLE 1. *Central circulatory responses at sea level, acute ascent, and 21 days of acclimatization at 4,300 m*

Exercise Time, min	Total $\dot{V}O_2$, ml/min	Cardiac Output, l/min	Heart Rate, beats/min	Stroke Volume, ml
		Sea level (751 Torr)		
0	271±7	5.1±0.3	62±4	83±6
5	1,726±48	15.2±1.0	123±6	126±12
15	1,809±71	16.2±0.8	129±5	125±4
30	1,832±54	15.3±0.9	136±5	113±7
45	1,850±60	15.9±1.4	140±5	114±6
		Acute ascent (463 Torr)		
0	289±12	5.2±0.4	72±4*	73±6
5	1,675±62	15.8±0.9	130±5*	124±7
15	1,757±101	16.6±1.1	141±3*	119±8
30	1,913±63	16.2±1.0	149±3*	109±6
45	1,923±69	16.2±1.4	152±3*	105±8
		Acclimatization (461 Torr)		
0	360±18*†	4.2±0.5	76±4*	57±9*
5	1,780±51	11.9±1.2*†	131±5*	91±9*†
15	1,813±55	11.7±1.3*†	139±5*	84±9*†
30	1,836±51	12.5±1.2†	148±5*	85±8*†
45	1,850±54	12.8±1.2*†	151±5*	84±7*†

Values are means ± SE. $\dot{V}O_2$, O_2 uptake; 0, rest. Stroke volume calculated as cardiac output/heart rate. * $P < 0.05$ by ANOVA for the same time period compared with sea level; † $P < 0.05$ by ANOVA for the same time period compared with acute ascent.

ml/min (75 ± 1% SL $\dot{V}O_{2\,max}$) on *day 7*, and 2,719 ± 79 ml/min (77 ± 1% SL $\dot{V}O_{2\,max}$) on *day 18* at 4,300 m. Thus there were no differences in $\dot{V}O_{2\,max}$ at 4,300 m. By design, $\dot{V}O_2$ was maintained at a constant level during submaximal exercise at SL and at 4,300 m altitude, being 1,804 ± 27 ml/min (51 ± 1% SL $\dot{V}O_{2\,max}$) at a work load of 101 ± 3 W, 1,817 ± 61 ml/min (67 ± 2%, of PP-5 $\dot{V}O_{2\,max}$) at work load of 97 ± 2 W, and 1,820 ± 15 ml/min (68 ± 1% of PP-5 $\dot{V}O_{2\,max}$) at a work load of 97 ± 3 W for SL, acute, and chronic altitude, respectively. Also, $\dot{V}O_2$ remained unchanged throughout the last 40 min of submaximal exercise, which confirms a steady state of whole body energy expenditure (Table 1). Blood temperature rose ~1.0°C between 5 and 45 min of exercise, with no significant difference between SL and 4,300 m.

On arrival at 4,300 m there was a significant increase in heart rate during exercise. This was not accompanied by an increase in cardiac output because of a trend toward a lower SV compared with SL. With acclimatization there was a 25% reduction in exercise cardiac output, entirely explained by a similar fall in SV (Table 1).

LBF was unchanged between SL and acute hypoxia, but decreased 18% as a result of acclimatization (Table 2). The percentage of cardiac output to both legs during exercise was similar to SL at both acute and chronic hypoxia without evidence of redistribution as a result of acclimatization (Fig. 1*A*). Leg $\dot{V}O_2$ was lower during submaximal exercise at high altitude compared with SL with no additional change as a result of acclimatization. The percentage of total body $\dot{V}O_2$ by the legs was lower at altitude with no influence from acclimatization (Fig. 1*B*). MAP tended to decrease somewhat with acute hypoxia but increased significantly with acclimatization.

Arterial P_{CO_2} at rest decreased from 40 ± 1 Torr at SL to 30 ± 1 Torr at acute hypoxia ($P < 0.05$) and 23 ± 1 Torr at chronic hypoxia ($P < 0.05$ compared with acute hypoxia). There was a marked fall in arterial P_{O_2} and O_2 saturation during exercise with acute hypoxia and partial restoration toward SL values with acclimatization (Table 3). Arterial O_2 saturation and Hb concentration both increased with acclimatization, resulting in marked elevations in arterial O_2 content. Because of the decreased arterial O_2 content on arrival and the unchanged blood flows, both total body and leg O_2 delivery were decreased (Fig. 2, *A* and *B*). After acclimatization, cardiac output and LBF decreased as arterial O_2 content increased, resulting in O_2 deliveries that were unchanged compared with arrival and lower than at SL. Total body and leg O_2 delivery behaved in a similar fashion.

Arterial Hct increased somewhat with acute hypoxia, but there was a prominent rise after acclimatization. Acute hypoxia resulted in a decrease in plasma volume and total blood volume. In contrast, acclimatization was associated with an increase in RBC volume that accompanied a fall in plasma volume, resulting in no overall change in total volume (Table 4).

Acute hypoxia resulted in no change in systemic vascular resistance at rest and during exercise, whereas there was a significant decrease in leg vascular resistance and an increase in leg vascular conductance, suggesting some local vasodilatation (Fig. 3). In contrast, acclimatization resulted in marked increases in systemic and leg vascular resistances, especially during exercise. These were accompanied by a decrease in leg vascular conductance.

Resting arterial NE was 0.56 ± 0.07 ng/ml at SL; it decreased to 0.35 ± 0.04 ng/ml with acute hypoxia ($P < 0.05$), but after acclimatization rose to 0.80 ± 0.05 ng/ml,

TABLE 2. *Physiological responses in the exercising leg at sea level, acute ascent, and 21 days of acclimatization at 4,300 m*

Exercise Time, min	Work Load, W	Leg $\dot{V}O_2$, ml/min	Leg Blood Flow, l/min	MAP, Torr
		Sea level		
0		34±5	0.47±0.1	86±4
5	101±3	562±59	4.4±0.4	105±4
15	101±3	625±50	4.6±0.3	102±4
30	101±3	627±49	4.6±0.3	100±3
45	101±3	619±47	4.5±0.2	98±5
		Acute ascent		
0		36±6	0.61±0.1*	87±4
5	97±2	526±44	4.6±0.3	95±6
15	97±2	473±31*	4.3±0.2	97±5
30	97±2	475±29*	4.3±0.2	95±6
45	97±2	521±25*	4.6±0.3	97±6
		Acclimatization		
0		40±4	0.55±4*†	110±4*†
5	97±3	493±31	3.5±0.2*†	112±6†
15	97±3	513±28*	3.7±0.2*†	110±6†
30	97±3	551±25	3.8±0.1*†	104±6
45	97±3	579±25	3.9±0.2*†	100±5

Values are means ± SE. MAP, mean arterial blood pressure; 0, rest. * $P < 0.05$ by ANOVA compared with sea level; † $P < 0.05$ by ANOVA compared with acute ascent.

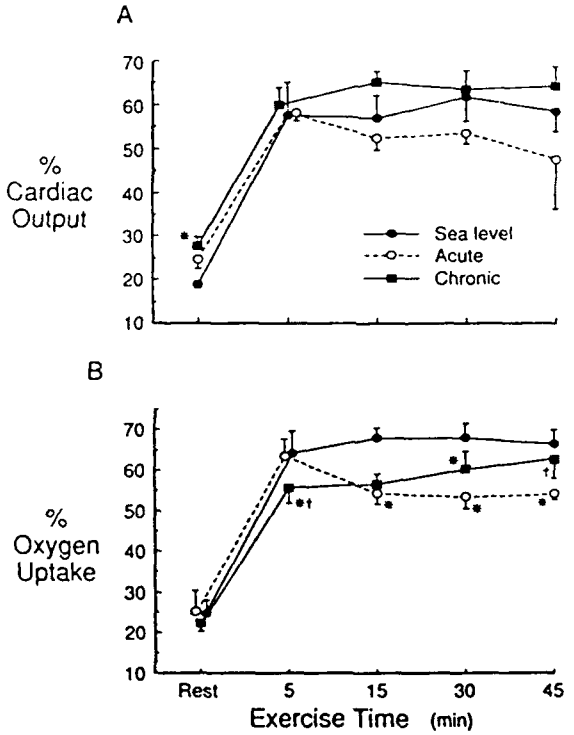

FIG. 1. *A*: percent cardiac output to both legs at rest and during exercise at sea level (SL) and acute hypoxia (Acute) and chronic hypoxia (Chronic). *B*: percent total O_2 uptake by both legs at rest and during exercise at SL and acute and chronic hypoxia. Values are means ± SE. * $P < 0.05$ compared with SL; † $P < 0.05$ compared with Acute.

which was significantly greater than both other values ($P < 0.05$). During exercise, the mean NE level averaged during 45 min was 2.08 ± 0.25 and 2.23 ± 0.12 ng/ml at SL and on arrival at altitude, respectively (P = NS), but rose ($P < 0.05$) to 2.85 ± 0.23 ng/ml with acclimatization. This represented a 28% increase in NE during exercise with acclimatization.

Overall, during exercise, acclimatization resulted in significant decreases in cardiac output, SV, and LBF; no changes in total blood volume; and marked increases in MAP, systemic and leg vascular resistances, and plasma NE levels (Fig. 4).

DISCUSSION

The results of this investigation support prior evidence that both cardiac output (2, 7, 13, 15, 18, 29) and LBF (3) during submaximal exercise are reduced with high altitude acclimatization. The unique aspect of this study is that both cardiac output and LBF were measured concurrently at various time points throughout the same absolute level of prolonged submaximal exercise. In this fashion, distribution of cardiac output to exercising and nonexercising tissues could be determined. In addition, these hemodynamic measurements were made in conjunction with the determination of arterial NE levels as well as resting blood volume. This was the first investigation that included the determination of all of the major factors potentially involved in the regulation of O_2 transport at high altitude. The findings suggest no redistribution of cardiac output between the exercising limb and other regions of the body during exercise performed with either acute or chronic exposure to hypoxia; thus central and peripheral blood flow responses occurred in parallel at the work load utilized. Both total body and leg O_2 transport remained constant over time at altitude, although lower than at SL. The decreases in blood flow offset the observed increases in arterial O_2 content, thereby resulting in no increase in O_2 transport as a result of acclimatization.

Throughout this investigation, $\dot{V}O_2$ during submaximal exercise remained constant. Thus total body O_2 transport was lower at both acute and chronic hypoxia than at SL despite a constant O_2 demand. In the leg, $\dot{V}O_2$ during exercise was lower at both acute and chronic hypoxia compared with SL despite a constant total body $\dot{V}O_2$. The work loads utilized at high altitude tended to be somewhat lower than at SL (Table 2) to maintain total body $\dot{V}O_2$ constant. This lower leg $\dot{V}O_2$ may reflect heightened $\dot{V}O_2$ by either nonexercising muscle beds or, more likely, the respiratory muscles, as the work of breathing at high altitude is greater than at SL (8). This decrease in leg $\dot{V}O_2$ probably contributed to the lower leg O_2 transport seen during both acute and chronic hypoxia; however, as noted in the central circulatory responses, the acclimatization process itself had a more profound effect.

There were no significant increases in either cardiac output or LBF during exercise with acute hypoxia compared with SL in this study. These findings differ from other studies of acute hypoxia where low concentrations of inspired oxygen are administered acutely and result in an increase in blood flow during exercise (23). The subjects in this study spent a night at an intermediate altitude of 1,954 m, which may have resulted in some early ventilatory adaptations. The resting arterial P_{CO_2} of 30 ± 1 Torr at acute hypoxia supports this explanation. De-

TABLE 3. *Arterial blood O_2 responses at sea level, acute ascent, and 21 days of acclimatization at 4,300 m*

Exercise Time, min	Arterial Hb, g/100 ml	Arterial O_2 Saturation, %	Arterial O_2 Content, vol%	Arterial P_{O_2}, Torr
		Sea level		
0	13.6±0.4	97±1	18.4±0.5	94±2
5	14.1±0.3	97±1	18.9±0.4	100±2
15	14.1±0.3	97±1	19.0±0.4	103±2
30	14.0±0.3	97±1	18.9±0.5	100±2
45	14.0±0.4	97±1	18.9±0.6	103±3
		Acute ascent		
0	13.8±0.2	81±1*	15.6±0.5*	41±1*
5	14.1±0.7	78±2*	15.5±0.5*	41±1*
15	14.3±0.2	75±1*	14.7±0.5*	40±1*
30	14.2±0.1	75±1*	14.6±0.6*	41±1*
45	14.0±0.2	77±2*	15.0±0.3*	41±1*
		Acclimatization		
0	15.4±0.3*†	87±1*†	18.8±0.5†	50±1*†
5	15.8±0.8*†	83±1*†	18.4±0.5†	49±1*†
15	15.7±0.3*†	81±1*†	17.7±0.4*†	48±1*†
30	15.7±0.3*†	81±1*†	17.8±0.4*†	48±1*†
45	15.8±0.3*†	80±1*†	17.7±0.4*†	47±1*†

Values are means ± SE. Hb, hemoglobin; 0, rest. * $P < 0.05$ by ANOVA compared with similar time at sea level; † $P < 0.05$ by ANOVA compared with acute ascent.

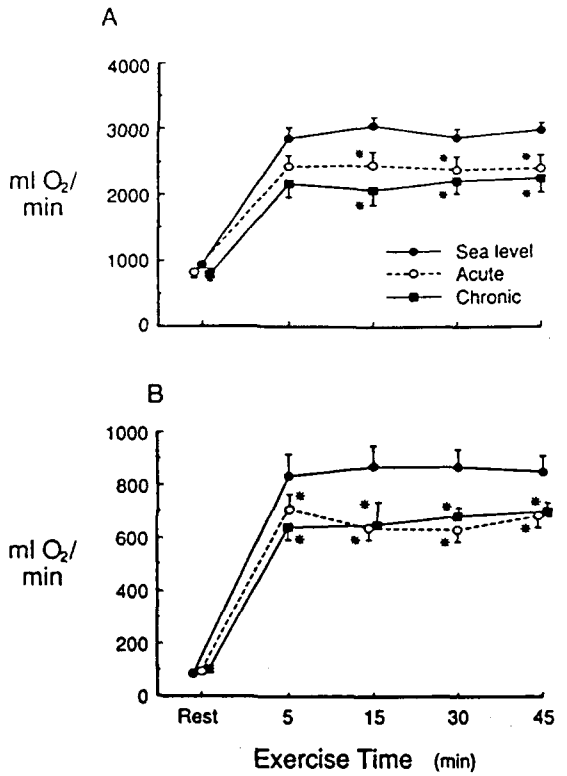

FIG. 2. *A*: mean total body O_2 delivery at rest and during exercise at SL and acute and chronic hypoxia. Total body O_2 delivery = cardiac output × arterial O_2 content. *B*: mean leg O_2 delivery at rest and during exercise at SL and acute and chronic hypoxia. Leg O_2 delivery = leg blood flow × arterial O_2 content. Values are means ± SE. *$P < 0.05$ compared with SL.

TABLE 4. *Blood volume responses at sea level, acute ascent, and 18 days of acclimatization at 4,300 m*

	Sea Level	Acute Ascent	Acclimatization
Arterial hematocrit, %	41.2±1.1	43.5±0.9*	50.2±0.9*†
RBC volume			
ml	2,399±77	2,399±77	2,877±141*†
ml/kg	33.3±0.9	32.7±0.8	40.2±1.2*†
Plasma volume			
ml	3,505±138	3,109±82*	2,869±152*
ml/kg	48.8±2.1	42.5±1.8*	40.2±1.2*
Total blood volume			
ml	5,896±203	5,509±131	5,732±273
ml/kg	82.0±2.9	75.3±2.4*	80.3±1.9†

Values are means ± SE. Blood volume at acute hypoxia was estimated from changes in hematocrit with the assumption that all effects were secondary to decreases in plasma volume. * $P < 0.05$ by ANOVA compared with sea level; † $P < 0.05$ by ANOVA compared with acute ascent.

spite this potentially early adaptation, there remained marked differences between the acute and chronic hypoxia testing periods, indicating marked effects of acclimatization on O_2 transport.

One of the potential mechanisms for the decreases in blood flow seen with acclimatization could be a decrease in total blood volume, thereby resulting in less cardiac filling and a lower SV. It is doubtful that cardiac dysfunction occurred, as none has been observed even at extreme altitude (20, 27). Prior studies have suggested that the decreases in cardiac output seen with acclimatization were related to reductions in plasma volume that resulted in lower right atrial pressures and smaller intraventricular volumes (1, 2). Despite these findings, there have been minimal improvements seen in exercise SV with volume expansion (2) and phlebotomy plus volume replacement (13) in subjects after acclimatization to moderate altitudes. In addition, chronic residents of moderate altitude attain improvements in cardiac output and SV after descent to SL without significant change in total

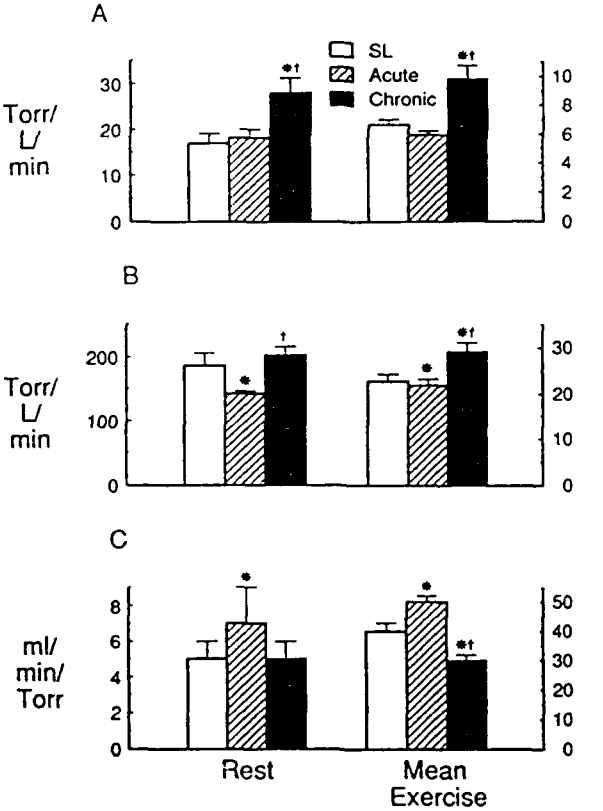

FIG. 3. *A*: mean systemic vascular resistance at rest and during exercise at SL and acute and chronic hypoxia. Exercise values were averaged over 45-min period. *B*: mean leg vascular resistance at rest and during exercise at SL and acute and chronic hypoxia. *C*: mean leg vascular conductance at rest and during exercise at SL and acute and chronic hypoxia. Values are means ± SE. *$P < 0.05$ compared with SL; † $P < 0.05$ compared with Acute.

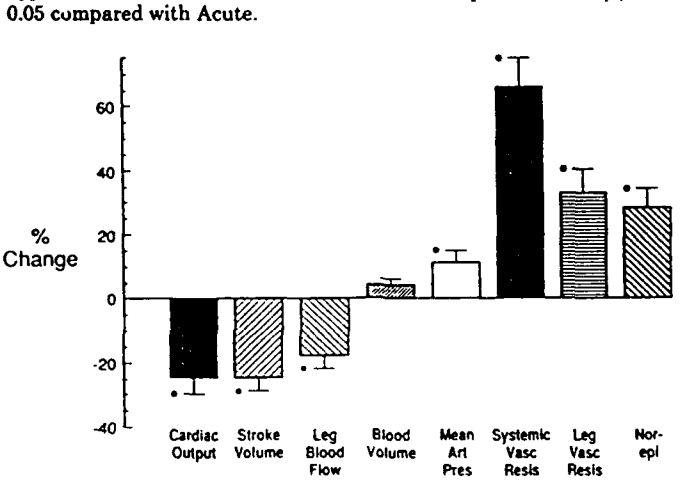

FIG. 4. Cardiovascular effects of acclimatization during submaximal exercise. Percentages were obtained from values at acute vs. chronic hypoxia. Values are means ± SE. *$P < 0.05$.

blood volume (12). The findings in the current study also question the importance of blood volume as the major determinant of the reduction in blood flow seen with acclimatization. The fall in plasma volume seen with acclimatization was offset by an increase in RBC mass. Thus resting total blood volume did not change significantly over time at 4,300 m, despite a 25% decrease in exercise SV. Although blood volume was not directly measured on acute ascent to altitude, the use of Hct as an indicator of changes in plasma volume was sufficient to determine the adaptation that occurred between acute and chronic hypoxia. Other studies have reported either a decrease (16) or no change (26) in total blood volume with acclimatization at moderate altitudes, although no hemodynamic measurements were made. The findings differ because of variable time at altitude, the methods used to determine blood volume, and the lack of detail concerning the fluid and nutritional intake of subjects. The current investigation differed from all these other studies because of the attention paid to the nutritional and metabolic status of the subjects (G. E. Butterfield, J. Gates, G. A. Brooks, J. R. Sutton, and J. T. Reeves, unpublished observations). Total body weight decreased only 3% during the 21 days at 4,300 m.

There was a marked increase in mean systemic arterial pressure, as well as increases in both systemic and leg vascular resistance, that accompanied the decreases in cardiac output and LBF seen with acclimatization (Fig. 4). Prior studies have also shown an increase in MAP with acclimatization to moderate altitude (3, 7, 24, 29, 30). The increases in both leg and systemic vascular resistances occurred in the setting of both a rise in MAP and a decrease in blood flow. Examination of leg vascular conductance revealed a marked difference between acute and chronic hypoxia (Fig. 3*C*). Although leg vascular conductance increased significantly on acute ascent to altitude, there was a marked decrease below both SL and acute hypoxia levels as a result of acclimatization.

These changes in vascular resistance and conductance are directly related to the acclimatization process, in which arterial O_2 content increases while blood flow decreases. Although arterial Hct increased only modestly from 43.5 ± 0.9 to 50.2 ± 0.9%, some increase in blood viscosity may have occurred. This increase in blood viscosity must be considered as a possible mechanism for the increase in vascular resistance seen with acclimatization. A prior animal study utilizing isovolemic exchange transfusions under normoxic conditions has shown parallel increases in whole blood viscosity and systemic vascular resistance as Hct was increased from 40 to 55% (6). These changes were recorded only at rest, not during exercise, and were not accompanied by an increase in MAP. Studies performed in dogs at 1,500 m, with the use of transfusions of whole blood to produce similar increases in Hb and Hct, did not result in an increase in systemic vascular resistance (17). Only when hematocrit was increased to 65% did cardiac output fall and systemic vascular resistance increase, whereas systemic O_2 delivery remained unchanged. Finally, studies using isovolemic transfusions of RBCs containing 100% met-Hb suggest that arterial O_2 content may be more important than blood viscosity in the regulation of blood flow and vascular resistance, especially during exercise (J. Lindenfeld, J. V. Weil, V. L. Travis, and L. D. Horwitz, personal communication). Despite this information, a contribution of increased whole blood viscosity to the elevation in vascular resistance seen with acclimatization must be considered. Although whole blood viscosity was not measured in this study, it is unlikely that the expected modest increase in blood viscosity could fully explain the 65% increase in systemic vascular resistance and the 33% increase in leg vascular resistance seen during exercise after acclimatization.

Active vasoconstriction resulting in an increase in vascular resistance may be the mechanism responsible for regulating blood flow in relation to arterial O_2 content with chronic hypoxia to maintain O_2 transport. The precise mechanism for this active vasoconstriction cannot be determined from the available data in this investigation. One potential cause for active vasoconstriction leading to increases in vascular resistance with acclimatization would be heightened sympathetic nervous activity. Plasma NE levels were elevated with chronic but not acute hypoxia in this study. This pattern of NE elevation with exposure to the hypoxia of high altitude differed from that of epinephrine and appeared to be linked to the increases observed in vascular resistance (R. S. Mazzeo, P. R. Bender, G. A. Brooks, G. E. Butterfield, B. M. Groves, J. R. Sutton, E. E. Wolfel, and J. T. Reeves, unpublished observations). Although plasma NE levels are only one indicator of sympathetic nervous activity, during exercise they are directly related to muscle sympathetic nerve activity (25). Although plasma NE levels have been shown to underestimate the presence of increased muscle sympathetic nerve activity during rest with acute hypoxia (23), this occurred primarily at more severe levels of hypoxemia than in the present study. Also, there was a poor correlation between individual muscle sympathetic nerve activity and physiological responses. With chronic hypoxia, especially during exercise, plasma NE elevation could reflect either enhanced release, spillover, or decreased clearance, especially in the lower blood flow state of chronic hypoxia. A prior study in rats at chronic hypoxia has demonstrated that clearance is unaffected and that the increased plasma levels of NE represent elevated sympathetic nervous system stimulation (14). Thus, in the human, the sympathetic nervous system may be activated at chronic hypoxia and may contribute to the increases in MAP and vascular resistances observed at rest and during exercise. By increasing the impedance to blood flow, vasoconstriction would result in a decrease in central and peripheral blood flow. In this fashion, O_2 transport is maintained at the same level as during acute hypoxia.

Thus our findings suggest that the regulation of both total body and leg exercise O_2 transport during chronic hypoxia occur in parallel, are related to the reduction in central and peripheral blood flow, and may be mediated by sympathetically driven vasoconstriction resulting in heightened vascular resistance and reduced conductance. Blood volume changes with acclimatization do not appear to have a major influence in this regulation. Further work is needed to define more precisely the role of

sympathetic stimulation in the adaptation of O_2 transport in chronic hypoxia.

We especially thank the staff of the Geriatrics Research, Education and Clinical Center of the Palo Alto Veterans Administration Medical Center for their help and support during the sea level portion of this study. We are grateful to the US Army Research Institute of Environmental Medicine and especially to Allen Cymerman for allowing us to use the US Army, Maher Memorial Research Laboratory on the Summit of Pikes Peak, CO. We also thank Radiometer, Copenhagen for their generous provision of the ABL 300 Acid-Base Laboratory and the OSM3 Hemoximeter and the American Edwards Laboratories for the donation of a model 9520 thermodilation cardiac output computer used in this study. We also thank George Swanson for the use of the Soltec recorder. The technical help of Laurie Trad, Joan Gates, and Stacy Storey was greatly appreciated.

This work was supported in part by National Heart, Lung, and Blood Institute Grant HL-14985.

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Received 4 December 1989; accepted in final form 18 October 1990.

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